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MAY 1953
VOLUME 69 NUMBER 5

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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Communications regarding subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY, American Medical Association, 535 North Dearborn Street, Chicago 10.

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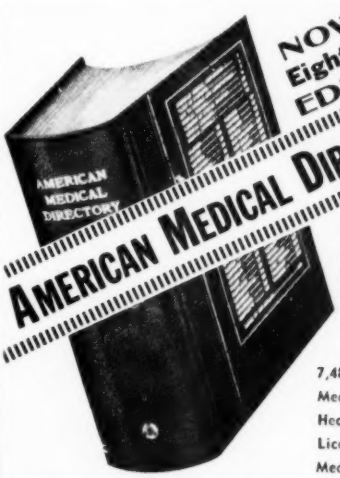

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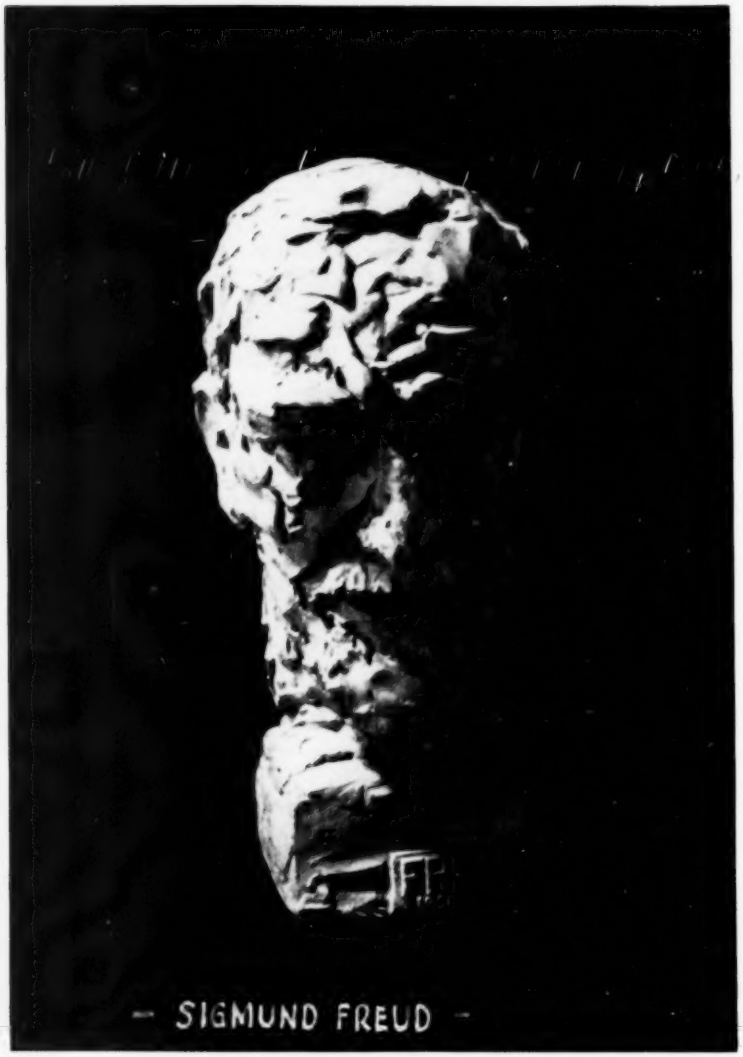

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CEREBRAL VASCULAR INSUFFICIENCY

An Explanation of Some Types of Localized Cerebral Encephalopathy

ELIOT CORDAY, M.D.
SANFORD F. ROTHENBERG, M.D.
AND
TRACY J. PUTNAM, M.D.
LOS ANGELES

ACUTE cerebral disturbances are usually considered to be the result of cerebral hemorrhage, thrombosis, embolism, or spasm.[1] Yet in 60 of 100 cases of fatal cerebral infarction Hicks and Warren [2] were unable to find evidence of mechanical occlusion of cerebral vessels by thrombosis, embolism, or arteriosclerosis. In other words, cerebral infarction without occlusion of the cerebral arteries may occur.

For many years the finding of cerebral infarction without cerebral arterial occlusion and the transiency and reversibility of various acute manifestations of cerebral dysfunction [3] have been explained on the basis of cerebral vascular spasm. At present there appears to be considerable doubt concerning the role of spasm of the cerebral arteries in the production of focal cerebral disorders.[4] The present study is not concerned with the problem of whether spasm of cerebral arteries may bring about cerebral disorders. Rather, it is desired to call attention to another mechanism by which acute cerebral disturbances may be brought about. We call this mechanism acute cerebral vascular insufficiency. This term is specifically restricted to indicate

Presented at the Annual Staff Meeting, Cedars of Lebanon Hospital, Dec. 18, 1952.

This study was financially assisted by Dr. and Mrs. Jules Stein and the Tracy J. Putnam Foundation, Inc.

From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Medicine, University of California School of Medicine at Los Angeles (Dr. Corday).

1. Charcot, J. M., and Bouchard, C.: Nouvelle récherches sur la pathologie de l'hemorrhagie cérébrale, Arch. Physiol. norm. et path. **1**:110, 1868. Bouchard, C., and Charcot, J. M.: A Study of Some Points in the Pathology of Cerebral Hemorrhage, English translation by T. J. Maclaglan, London, Simpkin, Marshall & Co., 1872. Zahn, W.: Untersuchung über Thrombose: Bildung der Thromben, Virchows Arch. path. Anat. **62**:81, 1875. Cohnheim, J.: Pathology of the Circulation, in Lectures on General Pathology, translated from the Second German edition by A. B. McKee, London, The New Sydenham Society, 1889, Sect. 1, pp. 215-216.

2. (*a*) Hicks, S. P., and Warren, S.: Infarction of the Brain Without Thrombosis: An Analysis of 100 Cases with Autopsy, A. M. A. Arch. Path. **52**:403, 1951; (*b*) Introduction to Neuropathology, New York, McGraw-Hill Book Company, Inc., 1950.

3. (*a*) Volhard, F., and Fahr, K. T.: Die Brightsche Nierenkrankheit: Klinik, Pathologie und Atlas, Berlin, Springer Verlag, 1914. (*b*) Westphal, K., and Bar, R.: Pathogenesis of Apoplexy: Pathologic Investigations, Deutsches Arch. klin. Med. **151**:1, 1926. (*c*) Oppenheimer, B. S., and Fishberg, A. M.: Hypertensive Encephalopathy, Arch. Int. Med. **41**:264, 1928.

4. Pickering, G. W.: Transient Cerebral Paralysis in Hypertension and in Cerebral Embolism, J. A. M. A. **137**:423, 1948. The Question of Cerebral Angiospasm, Editorial, Ann. Int. Med. **36**:129, 1952.

generally transient and reversible insufficiency of the cerebral blood flow, although the deleterious effect upon the brain may be permanent. Our interest in this subject was aroused by the observation of eight patients who presented clinical features of such a nature that we were impelled to investigate further the concept of cerebral vascular insufficiency.

The remarkable clinical pictures presented by these patients and the results of experimental investigations bring to mind the analogous syndrome of acute coronary insufficiency. Master and associates [5] and others [6] described and popularized the latter condition, which occurs when a disproportion exists between the blood supply of the myocardium and the requirements of the myocardium. In other words, there develops a localized (or generalized) functional inadequacy of the coronary circulation without actual vascular occlusion. The coronary arteries, even when narrowed by an arteriosclerotic process, are usually able to supply the demands of the resting heart. But when the requirements of the heart are increased by factors such as work, excitement, and tachycardia, or when the blood supply is reduced, as in shock or hemorrhage, a functional inadequacy of the coronary circulation occurs. Anginal pain, occasionally heart failure, and electrocardiographic changes may result and usually persist until the exciting factor is corrected. Friedberg and Horn [7] demonstrated that an attack of coronary insufficiency may actually result in patchy subendocardial necrosis of the myocardium. This is especially likely to occur if the coronary blood flow is not promptly restored to an adequate level.

It would appear that a condition closely analogous to coronary insufficiency can occur with respect to the cerebral arterial system. This condition may appropriately be called cerebral vascular insufficiency.

The following case which we observed will serve to illustrate some of the clinical phenomena which may result from cerebral vascular insufficiency. Other cases of a similar nature are discussed later.

Case 1.—L. H., a white man aged 68, who was hypertensive, suddenly lost the sensation of his right leg and within a few minutes was unable to move the extremity. His color had become ashen-pale, and his wife stated that he was perspiring profusely but that his skin was icy-cold. When seen by a physician 15 minutes later, the patient was found to be in a state of shock. His blood pressure was 65/50. He was pale, and his skin was cold and clammy. He had no sensation in the lower right extremity, and his patellar and ankle reflexes were hyperactive. The plantar response of the right foot was of the Babinski type. His other reflexes were normal. While awaiting an ambulance for transfer to the hospital, the patient vomited a large amount of bright-red and dark-red blood. The red blood cell count was 3,600,000; the hemoglobin concentration was 65%. This case indeed presented a strange diagnostic problem. Two disturbances were apparent—a cerebral and a gastric event.

The patient received a transfusion of 500 cc. of whole blood within one and one-half hours of the onset of the neurological symptoms. The blood pressure promptly rose to 160 systolic, and the signs of shock disappeared. When the state of shock had been corrected, all the neurological signs and symptoms disappeared. The Babinski response was no longer present.

5. Master, A. M.; Grubner, R.; Dack, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency with Myocardial Infarction from Coronary Occlusion, Arch. Int. Med. **67**:647, 1941. Master, A. M., and Jaffe, H. L.: Coronary Insufficiency and Myocardial Necrosis Due to Acute Hemorrhage, J. Mt. Sinai Hosp. **7**:26, 1940.

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7. Friedberg, C. K., and Horn, H.: Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, J. A. M. A. **112**:1675, 1939.

The diagnosis then became apparent. Cerebral vascular insufficiency had developed, owing to the hypotensive state, which resulted from the gastric hemorrhage. The hypotensive state was corrected within one and one-half hours. This resulted in a reversal of the focal cerebral changes, which were secondary to cerebral vascular insufficiency.

Many observers [8] have reported similar cases in which transient or permanent focal and generalized cerebral signs or symptoms occurred in the presence of inadequate cerebral arterial blood flow without actual occlusion or hemorrhage of a cerebral artery. Nevertheless, it appears that the concept of cerebral vascular insufficiency as applied to focal cerebral disturbances has never been clearly defined, nor has its mechanism been elucidated.

It is hoped that the anatomic, clinical, and experimental data to be described in this paper will serve to establish the concept of cerebral vascular insufficiency, particularly because of its significant therapeutic implications. The importance of recognizing this disorder lies in the fact that with prompt, appropriate therapy, its manifestations are usually quickly abolished and permanent cerebral damage may be prevented, while if the condition is not recognized or is mistreated, irreversible changes in the brain may occur.

ANATOMICAL CONSIDERATIONS

The nature of the cerebral arterial circulation can best be appreciated when it is recognized that the arterial supply of each cerebral hemisphere is independent of the arterial supply of the other. This fundamental characteristic is true not only of the carotid system, which supplies the anterior two-thirds of the hemispheres (and in some instances the posterior third in part), but also of the vertebral system, which supplies the posterior one-third of the hemispheres. It is, of course, true that a collateral circulation through the circle of Willis connects the two hemispheres, but it is essential to realize that the anastomotic vessels of this connecting system do not function under ordinary conditions.[9] Arterial blood from one hemisphere does not traverse the circle of Willis to the opposite hemisphere except when the arterial pressure in the opposite side is significantly lowered relative to the first side. This has been demonstrated repeatedly during carotid angiography. Under normal circumstances, when the arterial pressures of the two hemispheres are equal, radiopaque material injected into one internal carotid artery does not appear in the contralateral hemisphere.[9] On the other hand, when the arterial pressure in the contralateral hemisphere is lowered by temporary occlusion of the internal carotid artery on that side, then the injected material is usually seen in both hemispheres. Therefore, it would appear that the anastomoses joining the two cerebral hemispheres function only when there is a relative unilateral fall in arterial pressure.

With reference to the vertebral arterial system, since both vertebral arteries join to form a single vessel, the basilar artery, it might be expected that the flow in the posterior cerebral branches of the latter would be independent of the flow in either vertebral artery. However, it has been shown, again by arteriography,[9] that the flow in one vertebral artery is streamlined in such a way that it passes along the same side of the basilar artery and enters the homolateral posterior cerebral

8. (*a*) Westphal and Bär.[3b] (*b*) Engel, G. L.: Fainting: Physiological and Psychological Considerations, Springfield, Ill., Charles C Thomas, Publisher, 1950. (*c*) Hamilton, K. A.: Personal communication to the authors.

9. Egas Moniz: L'angiographie cérébrale, Paris, Masson & Cie, 1934.

artery with little or no diversion to the opposite side. Thus, the posterior portion of each cerebral hemisphere also appears to possess an independent arterial supply for its particular side. Under these circumstances, the nutrition of the posterior one-third of a cerebral hemisphere would seem to depend upon the adequacy of blood flow through a rather remote tributary, the homolateral vertebral artery.

PHYSIOLOGICAL CONSIDERATIONS

The significance of the lack of a dependable collateral blood supply from the opposite hemisphere when the flow through a single cerebral vessel is compromised by disease can be strikingly demonstrated by analogy with the phenomena which occur in a system of rigid tubes. For present purposes only two principles need be recalled: (1) The velocity of flow in a tube of given caliber is proportional to the pressure of the fluid, and (2) the pressure remaining constant, the volume of flow per unit time is proportional to the fourth power of the diameter of the tube, Poiseuille's law (Brew and Dill[10]). Assuming that relationships roughly approximating these are also valid for cerebral vessels, the second principle would mean that if the caliber of an artery were reduced by arteriosclerosis to half its normal value, the volume flow through this artery would be reduced to one-sixteenth its previous level, provided the pressure within the artery were maintained. If the pressure were reduced by any means at all, the reduction in volume flow would be reduced still more drastically. It is thus clear that the combination of localized narrowing in the arterial tree and hypotension can readily lead to severe ischemia of the area supplied by the involved vessel. If the hypotension is severe, the collateral circulation will also fail, thus further endangering the already ischemic region. It is quite possible for an artery narrowed to a moderate extent by arteriosclerosis or by congenital defect to carry on its function satisfactorily when the blood pressure is adequate; but if hypotension occurs, serious, and sometimes irreversible, damage to the brain cells may take place unless the pressure is promptly restored to an adequate level. Since cerebral arterial blood pressure is directly proportional to mean systemic arterial pressure, restoration of cerebral pressure must usually be accomplished by systemic measures.

The above considerations support the concept of focal cerebral ischemia, with or without actual infarction, resulting from an excessive hypotension confined to a single artery and its branches. This physiological abnormality, which we term cerebral vascular insufficiency, has not previously been clearly described, nor has much attention been directed toward its experimental elucidation.

The only previous direct experimental investigations of the effects of systemic (and hence, cerebral) arterial hypotension in the presence of occlusive cerebral arterial disease are those which were carried out by Thompson and Smith.[11] These observers occluded the middle cerebral artery in monkeys by means of a clip. When the systemic arterial pressure was maintained at a normal level after this procedure, no clinical, electroencephalographic, or pathological changes could be demonstrated in the experimental animals. However, when, after the middle cerebral artery was clamped, the blood pressure was reduced to half its normal level and maintained at

10. Brew, J. D., and Dill, L. V.: Rate of Blood Flow Through Standard Gage Needles Under Pressure, J. A. M. A. **140**:1145, 1949.

11. Thompson, R. K., and Smith, G. W.: Experimental Occlusion of the Middle Cerebral Artery During Arterial Hypertension, Tr. Am. Neurol. A. **76**:203, 1951.

this low level for one hour, signs of hemiplegia consistently developed, associated with distinct electroencephalographic abnormalities, and massive infarcts were found in the distribution of the occluded vessel. These clinical and pathological changes were, furthermore, severe and permanent. In these studies, the development of cerebral infarction would seem to result from inadequacy of the collateral circulation in the presence of hypotension. On the contrary, when the pressure was maintained at normotensive levels, the collateral blood flow was apparently capable of preventing the occurrence of significant ischemic changes in the region usually supplied by the occluded artery.

EXPERIMENTAL STUDIES

In order to study further the effect of changes in blood pressure in the presence of cerebral arterial occlusion, or partial obstruction, the following experiments were performed.

Method.—In each of four rhesus monkeys, under pentobarbital anesthesia (½ grain [0.032 gm.] of the drug per kilogram of body weight administered intravenously), the right internal carotid artery was partially obstructed to approximately one-fifth its original diameter with a Goldblatt clamp.[12] The femoral artery and vein of either the right or the left leg were dissected out, and a cannula was introduced into the artery. The cannula in the femoral artery was connected to a two-way stopcock. One end of the stopcock was connected to a mercury manometer for recording the systemic arterial pressure, and the other was used for withdrawal and reintroduction of blood. Heparin, in doses of 75 mg., was administered every two hours in order to prevent clotting.

After these procedures, control electroencephalographic tracings were obtained from the frontal and temporal areas. A Grass electroencephalograph was used in all experiments.

After a satisfactory control tracing had been recorded, the Goldblatt clamp was appropriately applied to obstruct partially the right internal carotid artery, and then a second electroencephalogram was obtained.

A state of systemic, and hence bilateral cerebral, hypotension was then created by withdrawing blood from the cannulated femoral artery. In order that the blood pressure should be reduced to a mean pressure of 20 to 30 mm. Hg (systolic, 40 to 50 mm.), it was necessary to withdraw 10 to 40 cc. of blood. When it was desired to restore the blood pressure to normotensive levels, the same blood was retransfused into the femoral artery, or saline or arterenol was injected.

During each phase (hypotensive and normotensive) of each experiment, electroencephalograms were made and observations of simultaneous blood pressure levels were recorded. Hypotensive states were created and corrected three or four times in each animal (total, 15 times), and the above-mentioned observations were made after each procedure.

Results.—When a state of cerebral hypotension was produced, the tracings showed dramatic changes. Most significantly, when the mean systemic pressure was brought to levels of 30 to 40 mm. Hg, the tracings from the incompletely ligated side showed a marked exaggeration of these responses, as compared with the much less striking abnormalities of the hemisphere whose blood supply had not been compromised (Figs. 1 to 4).

When the systemic and cerebral blood pressures were brought back to normal levels, the extreme abnormalities of the partially ligated side were entirely abolished, and the tracing returned to its base-line appearance, as did the opposite side (Figs. 1 to 4). These observations were carried out several times on each animal by repeat-

12. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischema, J. Exper. Med. **59**:347, 1934.

edly bringing the blood pressure down and then restoring it to normal levels. The results were consistent and reproducible at will. The recovery toward normal electric function appeared to be independent of the presence or absence of anemia. The critical factor in this connection would seem to be the height of the blood pressure per se, since the same phenomena were observed whether blood transfusion (Figs. 1 and 3), a pressor agent (Fig. 4), or isotonic saline solution (Fig. 2) was used to restore the pressure to normal levels.

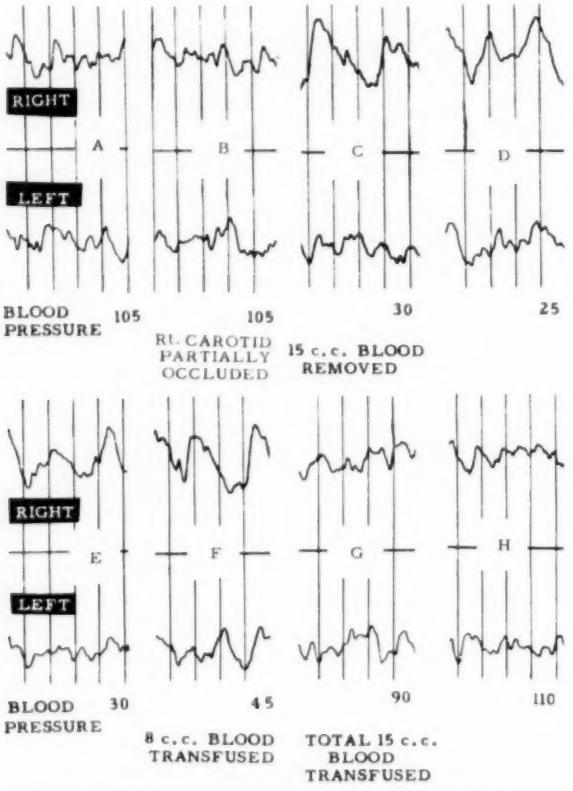

Fig. 1.—Electroencephalograms of a monkey before and after the right internal carotid artery had been partially occluded (*A* and *B*). When the blood pressure was reduced to hypotensive levels by bleeding, large slow waves appeared on the right side (*C*, *D*, *E*, and *F*). After transfusion and restoration of the blood pressure toward normal the electroencephalogram once again became normal (*G* and *H*). This procedure was repeated six times in this monkey. The experiment is a demonstration of cerebral vascular insufficiency.

These experiments clearly indicate that in the monkey systemic arterial hypotension results in greatly exaggerated electroencephalographic abnormalities in a cerebral hemisphere whose blood supply has already been compromised, as compared with the changes which occur during hypotension in a hemisphere whose blood supply has not been compromised (Figs. 1 to 4). Of equal, if not greater, significance is the demonstration that the exaggerated changes in the compromised side

produced by hypotension are completely reversible by restoring the blood pressure promptly to normal levels. The findings of these experiments are illustrated in Figures 1 to 4. It should be noted that the nature and degree of the electroencephalographic changes produced in these experiments are comparable to those obtained in animals with actual cerebral infarcts.[11]

The exaggerated electroencephalographic changes observed in the hemisphere with the ligated vessel during the hypotensive state consisted of one or more of the following: (*a*) pronounced increase of voltage (Figs. 1 to 3); (*b*) changes in frequency (Figs. 1 to 3); (*c*) washing out of waves (Fig. 4), and (*d*) depression of voltage (Fig. 4).

When the systemic blood pressure was brought to extremely low levels (10 to 20 mm. Hg), both hemispheres showed equally extreme electroencephalographic aberrations (Fig. 4). When the blood pressure was then raised by either transfusion

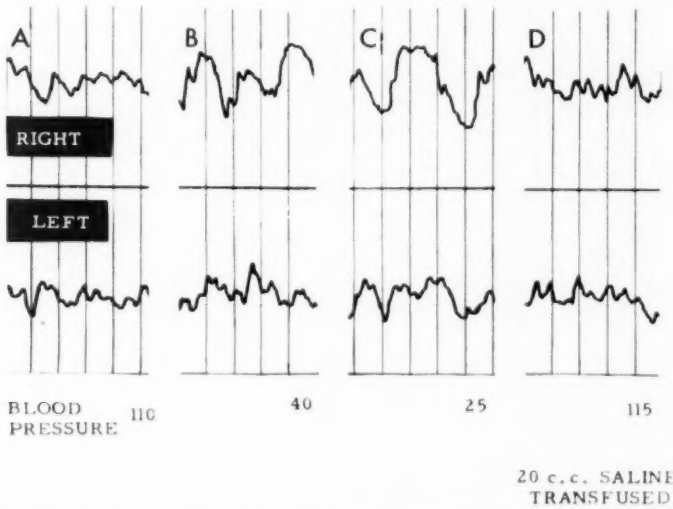

Fig. 2.—Electroencephalograms of a monkey after the right internal carotid artery had been partially occluded (*A*). When the blood pressure was reduced by bleeding (*B, C*), large slow waves developed on the right side. When 20 cc. of saline was run into the femoral artery under pressure and the blood pressure had returned to normal, the electroencephalogram once again became normal. This experiment demonstrates that the electroencephalographic changes of cerebral vascular insufficiency can be corrected if the blood pressure is restored to normal, even though the animal is still anemic.

or administration of arterenol or saline to somewhat higher levels (mean arterial pressure, 30 to 40 mm. Hg), the abnormalities of the ligated side only were distinctly exaggerated. When, finally, the blood pressure was further restored toward normal levels, the tracings of both sides reverted to the base line.

The exaggerated electroencephalographic effects of hypotension upon the hemisphere with a previously occluded blood supply were still further demonstrated by another experimental procedure. This consisted of ligating the main arterial

13. Footnote deleted.

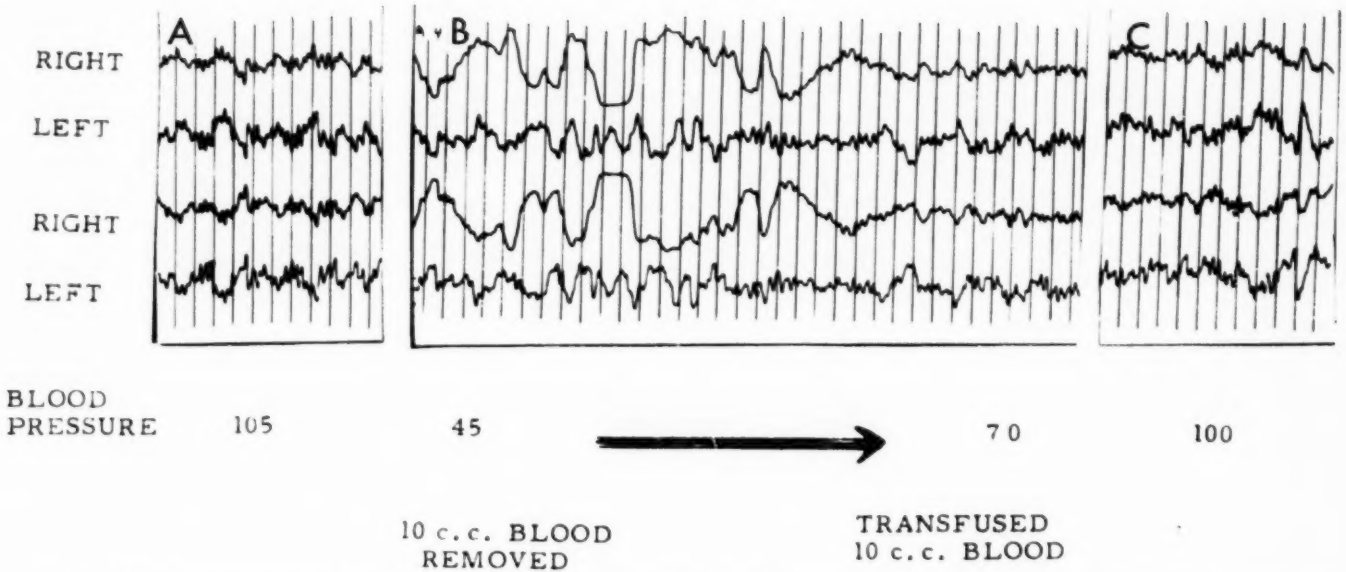

Fig. 3.—Electroencephalograms of a monkey after the right internal carotid artery had been partially occluded (*A*). When the blood pressure was reduced to 45 mm. Hg by bleeding the animal, large slow waves developed on the right side (*B*). When the blood pressure was restored to 70 mm. Hg by transfusing the animal with blood, the electroencephalogram returned toward normal. When the blood pressure returned to 100 mm., the electroencephalogram was completely normal (*C*).

supply of the right side, viz., the internal, external, and common carotid arteries and the subclavian arteries, just as has been described, and then compromising the collateral circulation from the left side by application of a Goldblatt clamp to the left common carotid artery. This device permitted a partial obstruction of the artery and almost certainly a reduction in blood flow to the left hemisphere.

When, under such a condition, a hypotensive state was induced by withdrawal of blood, the exaggerated electroencephalographic abnormalities of the right hemisphere were observed to be even more pronounced and to occur at significantly higher blood pressure levels (55 mm. Hg) than in the previous experiments. Nevertheless, these changes could be abolished at will by again restoring the systemic pressure to normal levels.

This experiment merely magnifies the effect of hypotension on a hemisphere with an obstructed blood supply. The already severe abnormalities produced in such a hemisphere by inadequacy of collateral circulation due to hypotension were still further accentuated by introducing a mechanical obstruction into the source of collateral flow.

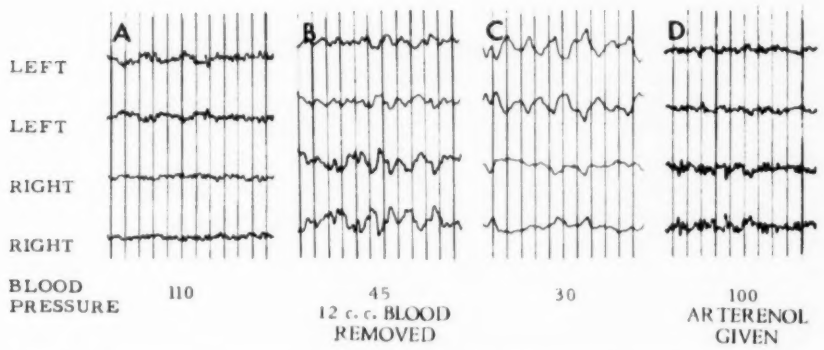

Fig. 4.—Electroencephalograms of a monkey after the right internal carotid artery had been partially occluded (*A*). When the blood pressure was reduced to 45 mm. Hg (*B*) by bleeding the animal, there were first an increased amplitude and then, at 30 mm. Hg, a depression of voltage and washing out of the brain waves on the right side (*C*). When the blood pressure was raised to 100 mm. Hg by intravenous administration of arterenol, the electroencephalogram returned to normal (*D*).

Summary and Interpretation of Experimental Findings.—With the electroencephalogram as a measure of cerebral disturbance, it was shown in monkeys that the advent of arterial hypotension resulted in much more marked abnormalities in the hemisphere whose blood supply had previously been partially or completely ligated than in the hemisphere on the unligated side. These exaggerated changes were found to be completely reversible by restoring the blood pressure to normal levels (Figs. 1 to 4). This reversibility was independent of the factor of anemia, since it was evident that the blood pressure was raised by a pressor drug or by saline, as well as by blood transfusion. If the blood pressure was brought to extremely low levels, very marked electroencephalographic abnormalities were produced in both hemispheres. If the blood pressure was then raised to a level of

moderate hypotension, the severe abnormalities in the unligated side promptly disappeared, while those of the partially ligated side persisted until the blood pressure approached normal levels.

These experimental results clearly indicated the crucial importance of the blood pressure level in the production and abolition of focal cerebral injury in areas with previously compromised arterial blood flow. It would appear that such areas may be able to function relatively satisfactorily in the presence of normal blood pressure. With the occurrence of hypotension, marked disturbances in cerebral function quickly make their appearance. If the hypotensive state is promptly corrected, the circulation again becomes adequate, and it is possible to abolish the evidences of cerebral dysfunction.

CLINICAL APPLICATIONS OF THE SYNDROME OF CEREBRAL VASCULAR INSUFFICIENCY

A considerable number of clinical cerebral phenomena whose pathogenesis has been obscure may now be better understood in the light of the concept of cerebral vascular insufficiency. The common denominator of these clinical pictures is the presence of cerebral hypotension.

The results of the experimental studies strongly suggest that localized narrowing, as a result of arteriosclerosis or congenital defect, will predispose the patient to focal neurological changes in the form of hemiplegia, hemianesthesia, etc., when a hypotensive state occurs. The immediate factor responsible for these focal cerebral changes is the deficiency of systemic blood pressure required to sustain the capillary blood flow necessary to permit adequate cerebral cell metabolism. When the blood pressure is normal, the capillary pressure distal to the incompletely obstructed vessel is sufficient to supply the demands of cellular metabolism.

The cells of the nervous system are particularly vulnerable to nutritional deprivation; their blood supply cannot long be withheld without the occurrence of severe and irreversible damage.

The complex requirements of cerebral cells are only incompletely known. In addition to oxygen, glucose, electrolytes, vitamins, and enzymes, there are many other factors necessary for their survival and proper function. Therefore it does not seem justified to ascribe gross focal disturbances in function to specific deficits, such as anoxia or anemia. In the present state of knowledge it would appear preferable to indicate the origin of such disorders by the more general term cerebral vascular insufficiency except in unusual instances in which a known qualitative or quantitative abnormality exists in the blood itself.

It is, of course, well known that general cerebral effects can result from systemic hypotension. These are manifested clinically by such symptoms as giddiness, syncope, and generalized convulsions. Such disorders often occur in the absence of cerebral vascular narrowing. It is probable, therefore, that a severer state of hypotension is required to cause such general changes than is necessary for the production of focal cerebral disorders in the presence of a previously localized vascular narrowing.

Other factors may bring about a state of localized cerebral dysfunction. These are qualitative changes in the blood stream, such as hypoxemia, hypoglycemia and anemia per se, without a hypotensive state being present. We are presently confining

our investigation to the changes of intracerebral blood pressure, because it is this phase which we have elucidated in the experimental animal.

Systemic hypotension of sudden onset may occur in the course of many and diverse conditions. From a consideration of the following clinical examples, it will be apparent that cerebral vascular insufficiency, either localized or generalized, may arise during periods of low systemic blood pressure of various origins.

Hypotension Due to Hemorrhagic Shock.—It has been known for centuries that the brain may be damaged as a result of hemorrhagic shock.[14] Case 1, described above, is a clear-cut example of transient localized cerebral vascular insufficiency which resulted from a severe gastric hemorrhage. While the blood pressure remained at shock levels, the patient exhibited focal cerebral signs. Immediately after the blood pressure was restored toward normal limits, these focal cerebral signs abated. Case 2 is an example of cerebral damage which resulted from irreversible shock due to severe gastric hemorrhage. Postmortem examination did not reveal any cerebral thrombosis or hemorrhage. The mechanism of cerebral injury due to systemic hemorrhage is not yet well understood.

Case 2.—O. O., a white man aged 52, with hypertension, had previously been admitted to the hospital for gastroenterostomy, at which time it was discovered that he had severe cirrhosis of the liver. He had been known to have diabetes for four years but did not require insulin.

The patient had a sudden episode of melena at 4 p. m. on Dec. 21, 1951; at 9 p. m. he vomited about 1,000 cc. of blood. His blood pressure immediately dropped to 80 systolic. He became pale, and his skin was clammy. He was rushed to the hospital, arriving at 10:30 p. m., and received a transfusion of 500 cc. of whole blood at 10:55 p. m. However, the blood pressure remained below 80 systolic until 2:30 a. m., when it rose to 116/70. At 4 a. m. the blood pressure was 126/56, and the systolic pressure remained above this level until 3 p. m. of that day. The patient vomited through the night and lost a total of 680 cc. of bloody vomitus, but otherwise he remained asleep. At 8 a. m. the red blood cell count was 3,910,000; the hemoglobin concentration 72%, and the platelet count, 179,860 per cubic millimeter. The prothrombin time was 33%. Urea nitrogen was 20.4 mg. per 100 cc.

During the morning of Dec. 22 the patient was lethargic and complained of a headache. He was a little confused. At 12 N. the patient had twitching of the legs while sleeping. At 2 p. m. the nurse noticed that the patient was comatose and that he did not respond to stimuli. At 3 p. m. the blood pressure was 165/80. At 3:15 p. m. he again vomited a large amount of dark-red blood. Neurological examination at 3 p. m. revealed nuchal rigidity, but a Kernig sign was not elicited. The patient had bilateral Babinski and Hoffmann signs. The reflexes were all hyperactive. Spinal puncture revealed clear, colorless fluid, under a pressure of 145 mm. Hg. The protein content was 35 mg. per 100 cc.; the cell count was 2 per cubic millimeter, all lymphocytes; the chlorides measured 765 mg. per 100 cc. He was given 50 cc. of whole blood and 3 grains (0.2 gm.) of aminophylline intravenously. At 7 p. m. the patient had purposeless movement and rigidity of the right arm. The following morning he presented incomplete paralysis of the left seventh cranial nerve and complete paralysis of the right upper extremity. Babinski and Hoffmann responses were elicited bilaterally. The patient remained in coma until he died. The blood sugar was 225 mg. per 100 cc. The hemoglobin was 65%, with a red blood cell count of 3,820,000. The CO_2-combining power was 25 mEq. The blood pressure rose to 214/92 and remained at that level until just before the patient died, on Dec. 26.

Postmortem examination revealed a bleeding stomal ulcer. The brain was normal except for marked narrowing of the cerebral vessels. The carotid arteries were patent. There was no evidence of cerebral thrombosis or hemorrhage.

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14. Hippocrates: Oeuvres Hippocratiques, edited by Littré Vol. 7, p. 111. Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1949. Hollenhorst, R. W., and Wagener, H. P.: Loss of Vision After Distant Hemorrhage, Am. J. M. Sc. **219**:209, 1950.

In this hypertensive patient the hypotension was caused by the stomal hemorrhage, which, in turn, was responsible for cerebral vascular insufficiency. Because of focal vascular changes (paralyses of the left facial nerve, of peripheral type, and of the right upper extremity) and the duration of the hypotensive state in this particular patient, the hemorrhage and cerebral vascular insufficiency resulted in irreversible cerebral changes.

Most authors [15] have considered spasm of the cerebral vessels the factor responsible for the cerebral damage after hemorrhage. Hollenhorst and Wagener [15] demonstrated that loss of vision and other neurological disorders could occur as a result of hemorrhage at a site remote from the eye. Fink [16] compiled from the literature 130 cases of acute transitory blindness which occurred post partum. Many other authors [15] demonstrated that transient visual disturbance and, at the same time, faintness, giddiness, and loss of consciousness often occurred as a result of hemorrhage. They reasoned that this was due to constriction of the retinal arterioles induced by the anemia and hypotension.

As a result of the experimental studies described above, the mechanism of injury to the brain and optic nerve from hemorrhage can now be explained on a basis of cerebral vascular insufficiency.

Hypotension Due to Coronary Shock.—Like Sugarman and Cole [17] and Hicks and Warren,[2a] we have demonstrated that the presenting, and sometimes the only, symptom of a coronary occlusion may be a cerebral event.

Case 3 is an instance of reversible cerebral vascular insufficiency due to hypotension following a massive myocardial infarction. Case 4 is an instance of cerebral infarction without cerebral artery thrombosis, which was caused by an unsuspected coronary artery occlusion. Both cases are instances of cerebral vascular insufficiency.

Case 3.—J. C., a white man aged 56, was admitted on May 5, 1952, with severe pain in the chest. An electrocardiogram revealed a recent myocardial infarction with a right bundle-branch block. The blood pressure on admission was 90/70. The pulse rate was 110 a minute. The patient's course was stormy for the next four days, owing to the occurrence of pericarditis. On May 18 the patient was feeling very well. His blood pressure was 140/100, and progress was very satisfactory. At 9 a.m. on May 19 the patient suddenly became pale and unconscious. His skin was cold and clammy, and the pulse rate was 120 a minute. The blood pressure was 40 mm. systolic. The patient did not respond to such stimuli as pressure on the eyeball and needle prick. Reflexes were not obtainable. The pupils were constricted and did not react to light. The conjunctival reflexes were present. There was no nuchal stiffness. Areflexia was present, with absence of the plantar response bilaterally. A spinal tap was performed immediately. The spinal fluid was under a pressure of 70 mm. and was colorless. The cell count was 8 per cubic millimeter; the protein measured 30 mg.; the sugar 70 mg., and the chlorides 730 mg. per 100 cc.

An intravenous transfusion of 1,000 cc. of isotonic saline solution with 2 cc. of levarterenol bitartrate (Levophed Bitartrate) was started immediately. Within 15 minutes the blood pressure rose to 110 mm. Hg. A few minutes later the patient responded to painful stimuli. Ten

15. Wolff, E.: Causation of Amblyopia Following Gastric and Other Haemorrhages, Tr. Ophth. Soc. U. Kingdom **55**:342, 1935. Hartmann, E., and Parfonry, J.: Cécité par perte de sang améliorée par l'acétylcholine mais conservant un rètrécissement binasal du champ visuel, Bull. Soc. opht. Paris, 1934, p. 56.

16. Fink, K.: Amaurosis Postpartum, Zentralbl. Gynäk. **48**:1118, 1924.

17. Cole, S. L., and Sugarman, J. N.: Cerebral Manifestations of Acute Myocardial Infarction, Am. J. M. Sc. **223**:35, 1952.

minutes after the blood pressure had risen to this level, he became fully conscious. His reflexes returned, with normal plantar response. At 3 p. m. the patient again went into a state of shock and again became comatose. This time he did not respond to blood transfusions or to any pressor drugs. He died at 9:15 p. m.

Autopsy revealed occlusion of the anterior coronary artery. The brain was normal except for generalized arteriosclerosis. The carotid arteries were patent.

This patient had generalized cerebrovascular insufficiency due to cardiogenic hypotension. When the blood pressure was raised, the neurological signs cleared. However, with the appearance of an irreversible hypotensive state, a state of irreversible cerebral vascular insufficiency developed.

CASE 4.—R. L. M., a white man aged 52, had apparently been in good health, although his systolic blood pressure was usually slightly elevated. On Dec. 29, 1950, at 11:45 p. m. his wife returned home to find him lying comatose in bed. When first seen by his physician, 45 minutes later, he was comatose and obviously in shock. He was pale and perspired profusely. The blood pressure was 75/60. An electrocardiogram taken at the time revealed no significant abnormalities. He was immediately transferred to the hospital, and a neurological consultation was obtained at 1:30 a. m. He was still completely unconscious; very painful stimuli could not elicit any response. The pupils were pinpoint; respiration was stertorous. All muscles were flaccid, and all reflexes were absent. The fundi showed clear margins. The skin was cold. The blood pressure was 60 systolic. The pulse rate was 120 a minute; the temperature, 96.6 F. The spinal fluid was under a pressure of 80 mm., with normal dynamics and was clear and colorless; the cell count was 3 per cubic millimeter, all lymphocytes; the protein measured 27 mg., the chlorides 740 mg., and the sugar 75 mg., per 100 cc.

A diagnosis of thrombosis of the basilar artery was made. At 9 a. m. on Dec. 30 his condition was much the same. The blood pressure remained below 80 systolic.

The patient was given a transfusion at 6 p. m. of Dec. 30 (18 hours after onset of coma), but this had no effect in raising the blood pressure. His condition was considered critical. The pupils were dilated from the mydriatic but did not react to light. The blood pressure was 70/40. He continued in this terminal phase until Jan. 2, 1951, when he died. The blood pressure remained below 80 systolic despite all attempts at raising it with blood plasma and nikethamide. No localizing signs developed, and all reflexes remained absent. A final clinical diagnosis of cerebral thrombosis of the basilar artery was made. At autopsy the brain appeared normal. The carotid arteries were patent. No evidence of cerebral thrombosis or hemorrhage was found, to the surprise of the clinicians. The left descending coronary artery was found to be recently thrombosed. Generalized arteriosclerosis was noted throughout the body.

The hypotension was evidently secondary to the myocardial infarction, causing cerebral vascular insufficiency. The hypotensive state could not be corrected, and this resulted in permanent generalized cerebral vascular insufficiency.

Cole and Sugarman [17] described the case of a man aged 57 with hypertension, who had previously recovered from transient left facial paralysis and left hemiplegia. The patient suddenly became unconscious; he had a recurrence of the left facial paralysis, and later right hemiplegia developed. He became disoriented and died. Electrocardiograms were not taken because the signs and symptoms appeared to be purely cerebral. Autopsy revealed a fresh myocardial infarction. The left cerebral hemisphere was somewhat soft and cystic. There were pronounced atherosclerotic changes, but no evidence of fresh thrombus, hemorrhage, or embolus was found in the brain.

Various authors explain the cerebral infarction which often occurs in coronary artery occlusion as due to cerebral vascular spasm; actually the cause of the cerebral

infarction (without occlusion of the cerebral artery) is a drop in systemic blood pressure or reduction in cardiac output following the myocardial infarction. It is a manifestation of cerebral vascular insufficiency.

Hypotension Due to Antihypertensive Drugs.—In a recent article, Grimson and his co-workers [18] recommended that caution be used with regard to the actions of adrenolytic and sympatholytic ganglion-blocking agents used in the treatment of hypertension. Hexamethonium and hydralazine (Apresoline) are potent drugs capable of causing marked reduction in arterial blood pressure. Grimson pointed out that the drop in blood pressure might be sufficient to cause serious effects in various organs. One of his patients had recurring episodes of hemiparesis and hemianesthesia, lasting an hour or more, during periods of hypotension. The symptoms resembled those of a previous episode of left hemiparesis. Similar changes have been described in arteriosclerotic heart disease when these antihypertensive agents are used.[18] This is a manifestation of focal cerebral vascular insufficiency.

Postural syncope with associated electroencephalographic changes has been shown to occur in patients tested with sodium nitrite.[19] Sodium nitrite is believed to lead to a significant decrease in venous tone, with resultant pooling of blood in dependent portions of the body. Undoubtedly, cerebral vascular insufficiency occurs and results in a loss of consciousness and fainting. High-voltage slow waves, similar to those of Figure 1, appear in the electroencephalogram during this state of cerebral vascular insufficiency.[19b]

Postural Hypotension.—In normal subjects an adequate cerebral circulation, despite changes in posture, as from the horizontal to the vertical position, is maintained by mechanisms which insure an equitable distribution of blood. An increase in peripheral vasoconstriction occurs, particularly in the arterioles of the splanchnic area and the skeletal musculature. Impairment of the capacity for postural adaptation as a result of the failure of these factors favors development of orthostatic circulatory insufficiency, with stasis of blood in dependent areas and a reduction of cerebral blood supply. As a rule, this defect is temporary and occurs in patients weakened by illness. Fall in the blood pressure and narrowing of the pulse pressure result in syncope after assumption of an erect posture. The symptoms are usually mild but may in some instances be extreme and persistent.

Thomas [20] described a remarkable case of a patient with arteriosclerosis and postural hypotension who had transient episodes of right hemiplegia in the erect posture. The occurrence of hemianopsia and aphasia in a patient with postural hypotension has been reported by Allen and Magee.[21] These authors attribute these symptoms to sclerosis of the cerebral vessels. Baker [22] has shown that patchy scle-

18. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., Jr., and Sieber, H. A.: Caution with Regard to Use of Hexamethonium and "Apresoline," J. A. M. A. **149**:215, 1952.

19. (*a*) Engel.[8b] (*b*) Forster, F. M.; Roseman, E., and Gibbs, F. A.: The Electroencephalogram Accompanying the Hyperactive Carotid Sinus Reflex and Orthostatic Syncope, Arch. Neurol. & Psychiat. **48**:957, 1942.

20. Thomas, H. M., Jr.: Transient Paralysis from Postural Hypotension, Bull. Johns Hopkins Hosp. **65**:329, 1939.

21. Allen, E. V., and Magee, H. R.: Orthostatic (Postural) Hypotension with Syncope, M. Clin. North America **18**:585, 1934.

22. Baker, T. W.: Recognition of Orthostatic Hypotension: Report of Case, Proc. Staff Meet., Mayo Clin. **13**:169, 1938.

rosis of the brain and the spinal cord might be the result of the intermittently disturbed circulation of these organs incident to postural changes in arterial pressure. These pathological changes may be analogous to the patchy necrotic changes in the heart in coronary insufficiency demonstrated by Horn and Finkelstein.[23]

Spingarn and Hitzig [24] reported a case of Addison's disease in which orthostatic circulatory insufficiency occurred. It is remarkable that Addison mentioned orthostatic weakness and syncope in his first report.[24]

Chew, Allen, and Barker [25] found neurological signs in 23% of their cases of orthostatic hypotension. Ellis and Haynes, in an article on postural hypotension, reported six cases, in four of which there was definite evidence of neurological disease, and an additional case in which there was probable involvement of the central nervous system.

Thus, it appears likely that postural hypotension can produce local and generalized circulatory disturbances in the arteriosclerotic or congenitally anomalous brain and give rise to the syndrome of cerebral vascular insufficiency.

We have studied an interesting patient with orthostatic hypotension and recorded electroencephalographic tracings during the syncopal attacks.

Case 5.—A white man aged 86 complained of dizziness and a feeling of great weakness and numbness of the extremities on assuming the erect posture. His blood pressure, while he was lying down, was 102 mm. Hg. When he stood up, it dropped to 50 mm. Hg, and after 80 seconds it returned to about 100 mm. Hg. While the blood pressure was down at such low levels, he was very unsteady in his gait and complained that he was sure he was going to topple over. Electroencephalograms taken before, during, and after the episode of orthostatic hypotension are shown in Figure 5. The electroencephalogram demonstrates large slow waves during the hypotensive state, similar to those in our experiments on the monkey. This is a clear example of the effect of generalized cerebral vascular insufficiency.

Hypotension Associated with the Carotid Sinus Syndrome.—Weiss and Baker [26] described three types of carotid sinus syncope. The first type, which they believed to be due to a vasodepressor reaction, is characterized by a drop in blood pressure. In the second type a cardioinhibitory carotid sinus reflex occurs, resulting in cardiac asystole. In the third, or cerebral, type neither a vasodepressor nor a cardioinhibitory response develops, and no fall in blood pressure is noted. The symptoms of all three types of carotid sinus syncope are similar.

Askey [27] described six patients in whom hemiplegia followed stimulation of the carotid sinus. One patient for years had had spontaneous transient attacks of right hemiplegia and dizziness. In this patient right hemiplegia was reproduced by stimulation of the left carotid sinus. It is not stated whether there was a drop in blood pressure.

23. Horn, H., and Finkelstein, L. E.: Arteriosclerosis of the Coronary Arteries and Mechanism of Their Occlusion, Am. Heart J. **19**:655, 1940.

24. Spingarn, C. L., and Hitzig, W. M.: Orthostatic Circulatory Insufficiency: Its Occurrence in Tabes Dorsalis and Addison's Disease, Arch. Int. Med. **69**:23, 1942.

25. Chew, E. M.; Allen, E. V., and Barker, N. W.: Orthostatic Hypotension: Report of 6 Cases and Review of Literature, Northwest Med. **35**:297, 1936.

26. Weiss, S., and Baker, J. P.: Carotid Sinus Reflex in Health and Disease: Its Role in Causation of Fainting and Convulsions, Medicine **12**:297, 1933.

27. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, Am. Heart J. **31**:131, 1946.

Engel, Romano, and McLin,[28] and others [29] performed electroencephalographic and electrocardiographic studies on patients with certain types of syncope, including carotid sinus syncope. These investigators demonstrated that in some patients

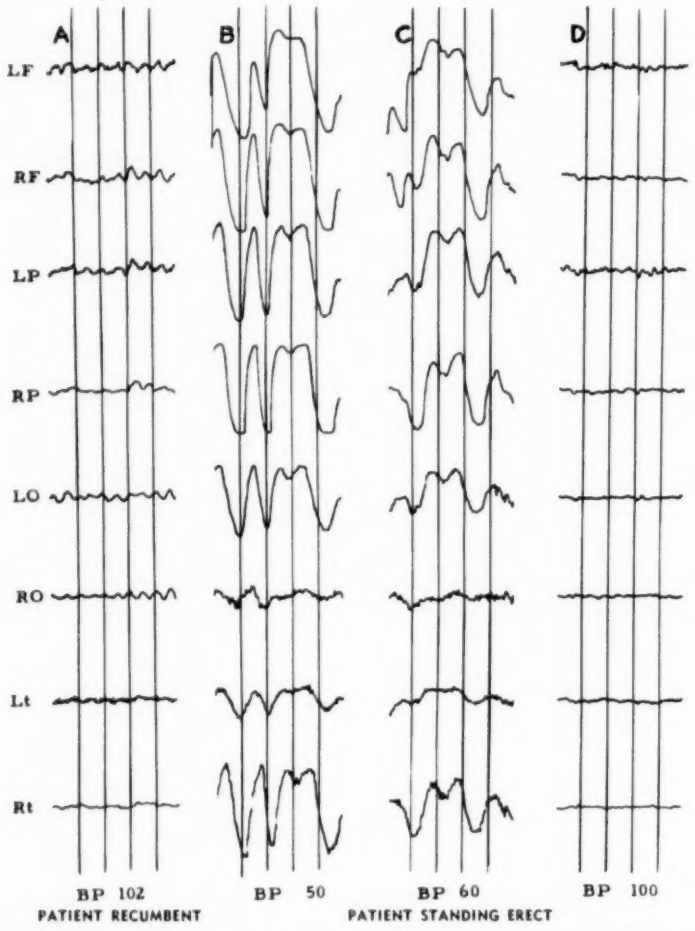

Fig. 5.—Electroencephalograms of a man aged 86 who complained of dizziness and a feeling of great weakness and numbness of the extremities on assuming an erect position: *A*, record while the patient was recumbent, with the blood pressure 102 mm. Hg; *B* and *C*, electroencephalograms with large slow waves, taken on his assuming the erect position, when the blood pressure dropped to 50 and 60 mm. Hg; *D*, return of electroencephalogram to normal when the blood pressure returned toward normal, 80 seconds after his assuming the erect position. This study is a demonstration of generalized cerebral vascular insufficiency.

28. Engel, G. L.; Romano, J., and McLin, T. R.: Vasodepressor and Carotid Sinus Syncope: Clinical, Electroencephalographic and Electrocardiographic Observations, Arch. Int. Med. **74:** 100, 1944.

29. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, J. Neurol., Neurosurg. & Psychiat. **1:**211, 1938.

stimulation of the hypersensitive carotid sinus resulted in reflex asystole of eight seconds' duration, with complete loss of consciousness, and falling, followed by clonic movements. The electroencephalogram demonstrated large-voltage slow waves during the episode of unconsciousness. There was a marked drop in blood pressure during the cardiac arrest. This drop in blood pressure probably accounted for the electroencephalographic changes. In other words, a state of generalized cerebral vascular insufficiency occurred.

Hypotension Due to Other Vasodepressor Phenomena.—Engel and associates [30] have studied numerous patients with vasodepressor syncope. In many cases they recorded electroencephalograms during the hypotensive state. Among the vasodepressor conditions studied were pain, hyperventilation, emotional factors, and distention of a viscus, e. g., the vagina or stomach. They have demonstrated patients with vasodepressor syncope, provoked by distention of the vagina. Electroencephalograms taken at the time of syncope revealed high-voltage slow waves. Engel and his co-workers also showed high-voltage slow waves in the electroencephalogram which occurred simultaneously with complete loss of consciousness produced by distention of the stomach or colon with air, and also in the electroencephalogram taken during vasodepressor syncope due to venipuncture. In all instances of the latter a marked drop in blood pressure occurred. Complete unconsciousness, characterized by unawareness, muscular relaxation, and falling, was accompanied by high-voltage slow waves in the electroencephalogram, regardless of the mechanism by which the unconsciousness was provoked. Less extreme changes in consciousness, such as lightheadedness, giddiness, and transient unconsciousness, were associated with less obvious slowing in the electroencephalogram.

Generalized cerebral vascular insufficiency occurs as a result of various vasodepressor phenomena. It is conceivable that focal cerebral signs of cerebral vascular insufficiency could develop in patients with impairment or anomalies of the cerebral circulation associated with these vasodepressor phenomena.

Hypotension Due to Surgical Procedures and Anesthetics.—The occurrence of cerebral complications following surgical procedures has been noted by many observers. For example, Behrend and Riggs [31] and Courville [32] have reported postoperative coma, convulsions, psychic disturbances, and focal cerebral disorders. In cases in which autopsy was performed evidence of cerebral vascular occlusion was not found.

While it is difficult in such cases to differentiate between the effects of hypoxia due to an anesthetic and the results of hypotension occurring during the operative procedure, it would appear probable that some of these disturbances arose as a consequence of a fall in systemic blood pressure. This would seem especially likely in cases in which a spinal anesthetic was administered.[33]

Cardiac Surgery.—With the advent of valvular surgery of the heart, numerous instances of decerebrate rigidity, hemiplegia, and paraplegia have occurred. Most

30. Engel, Romano, and McLin.[28] Engel.[5b]

31. Behrend, A., and Riggs, H. A.: Cerebral Complications Following Surgical Operation: Prevention and Treatment, Am. J. Surg. **53**:286, 1941.

32. Courville, C. B.: Pathogenesis of Necrosis of the Cerebral Gray Matter Following Nitrous Oxide Anesthesia, Ann. Surg. **107**:371, 1938.

33. Walter, L.: Hemiplegia Following Spinal Anesthesia, Am. J. Surg. **53**:359, 1941.

authors feel that these complications are due to an embolus which has been pushed forth into the blood stream from the left atrium, to the mechanical interruption of the blood flow through the orifice of the mitral valve, or to the occurrence of ventricular arrhythmias during the surgical procedure, so that insufficient blood reaches the cerebral hemispheres.

Postsympathectomy Cerebral Vascular Insufficiency.—Various authors [34] have alluded to the occurrence of stroke in the wake of the precipitous induction of postsympathectomy hypotension. Here, again, the focal neurological changes must have been induced by the state of cerebral vascular insufficiency secondary to hypotension.

Cerebral Vascular Insufficiency Syndrome Due to Trauma.—Numerous articles refer to cases in which cerebral disorders have been manifested during periods of shock, only to have a return to normal after the state of shock had been reversed. These are obvious instances of reversible cerebral vascular insufficiency.

Cerebral Vascular Insufficiency Due to Other Cardiac Disease.—It has been already demonstrated that cerebral vascular insufficiency can occur as a result of myocardial infarction. Instances of cerebral and generalized focal changes have been demonstrated in other cardiac conditions.

(*a*) Cardiac Arrhythmias: Auricular arrhythmias seldom cause syncope unless the ventricular rate is above 180 per minute. The rate is seldom above 180 per minute. The cause of the syncope is probably due to the reduction in cardiac output. It is conceivable that if the cerebral vessels are narrowed focal signs of cerebral vascular insufficiency will develop. Comeau [35] observed a patient in whom syncope developed during the change of rhythm from regular sinus rhythm to auricular fibrillation. He stated that the syncope is probably due to the drop in blood pressure, which results from the asystole which intervenes in the 15- to 20-second period before the second rhythm takes over. We have observed a patient who had syncope and then convulsions on the left side each time the rhythm converted from regular sinus rhythm to auricular fibrillation. No residual neurological signs were noted.

Schwartz and Jezer [36] studied the syncopal convulsive seizures which developed in a patient with paroxysmal attacks of ventricular fibrillation. The convulsive seizures were probably due to the drop in blood pressure which occurred during the paroxysm of ventricular fibrillation.

The Adams-Stokes syndrome occurs oftenest in patients with complete heart block in whom the ventricular rate is below 40 beats per minute.[37] Convulsions are very common in the syncope resulting from the sudden changes in functional capacity of the ventricles.

Engel [5b] described focal neurological signs which may persist for hours in patients who have experienced episodic cardiac arrest. He stated that cerebral

34. Rabwin, M. H.: Personal communication to the authors.

35. Comeau, W. J.: Mechanisms for Syncopal Attacks Associated with Paroxysmal Auricular Fibrillation, New England J. Med. **227**:134, 1942.

36. Schwartz, S. P., and Jezer, O.: Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, Am. Heart J. **9**:792, 1934.

37. Nathanson, M. H., and Miller, H.: Mechanism of Syncope and Action of Drugs in Complete Heart Block, California Med. **76**:370, 1952. Stokes, W.: Observation on Some Cases of Permanently Slow Pulse, Dublin Quart. J. M. Sc. **2**:73, 1846.

softening may result from prolonged asystole. He states that during the period of unconsciousness the electroencephalograms show high-voltage slow waves.

(*b*) Congestive Heart Failure: Fishberg [38] described the patient in whom hemiplegia developed during episodes of congestive heart failure. The hemiplegia cleared up when the heart failure was corrected. We have seen one patient who had hemiplegia after an episode of congestive heart failure. This could be due to a drop in cardiac output or to the stagnant anoxia which occurs in congestive heart failure when there already is narrowing of cerebral vessels. The brain requires one-sixth of the cardiac output and 20% of the total bodily oxygen consumption. A qualitative change in the cerebral blood flow, such as anoxia, could thus account for the aforementioned findings, although the quantitative difference (hypotension) in congestive heart failure might have contributed to the state of cerebral vascular insufficiency.

Surgical Ligation of the Carotid Arteries.—Rather than systemic causes, a local cause of cerebral vascular insufficiency may exist, and this, too, in the nature of a local cerebral hypotensive state with resultant ischemia. A clear example of this follows.

CASE 6.—A man aged 45, with a right carotid artery-cavernous sinus fistula, had a complete surgical occlusion of his right common carotid artery and an incomplete obstruction of his right internal carotid artery, with local anesthesia. He was observed for 30 minutes with ligatures in place, without incident. Eight hours later the patient was found semicomatose with complete left hemiplegia. The patient was returned to the operating room, where the ligature on the right internal carotid artery was removed. Within one hour the left hemiplegia had vanished, and the patient became fully alert and ambulatory the next morning. After ligation of the common carotid artery the homolateral hemisphere is predominantly dependent on its blood supply via the retrograde flow from the external to the internal carotid artery. Should this resultant retrograde flow be further compromised by partial obstruction of the internal carotid artery, the pressure gradient will thus be lowered, and in this particular case it was insufficient to supply this hemisphere. However, with release of the ligature, the resultant blood-pressure gradient was both sufficient and efficient.

Chronic Occlusion of the Internal Carotid Artery or Basilar Artery.—Denny-Brown and others [39] have published numerous reports of transient focal cerebral signs due to chronic occlusion of the carotid or basilar arteries. The cerebral disorders were precipitated by a hypotensive state and disappeared when the blood pressure returned to normal, being clearly the result of cerebral vascular insufficiency.

CONCLUSIONS

It is the purpose of this paper to establish a new entity only vaguely recognized by authors in the past, namely, cerebral vascular insufficiency.

This transient condition has been demonstrated by experiment. Electroencephalograms were taken after the carotid vessels were partially or completely ligated in the monkey. When the blood pressure was lowered by bleeding the animal, focal electroencephalographic changes occurred on the side of the ligation, similar to those found in hemiplegia. When the blood pressure was restored, the electroencephalo-

38. Fishberg, A. M.: Heart Failure, Ed. 2, Philadelphia, Lea & Febiger, 1940.

39. Denny-Brown, D. E.: The Changing Pattern of Neurologic Medicine, New England J. M. **246**:839, 1952; The Treatment of Recurrent Cerebrovascular Symptoms and the Question of "Vasospasm," M. Clin. North America **35**:1457, 1951.

graphic records returned to normal. These changes were proved to be due to a drop in blood pressure, rather than purely to anemia.

Clinically, cerebral vascular insufficiency occurs in hemorrhagic shock, coronary shock, surgical and traumatic shock, hypotension due to sympathetic block, and Smithwick sympathectomy, postural hypotension, carotid sinus stimulation, spinal anesthesia, and cardiac surgery. It also can occur as a result of miscellaneous extracranial factors, such as surgical ligation of the carotid arteries, spontaneous thrombosis of the internal carotid artery (Denny-Brown syndrome), gravitational states, as in flying, and the use of antihypertensive drugs. The changes which occur are transient if the blood pressure is restored to normal within a short period. The electroencephalographic changes and symptoms of cerebral origin, such as hemiplegia and hemianesthesia, will then usually disappear. If the blood pressure is not promptly restored to normal in patients with cerebral arteriosclerosis or congenital anomalies, focal changes will be permanent. As in the heart in which coronary arteriosclerosis has occurred, it is important to maintain the cerebral blood pressure at normal levels, especially in the elderly patient with narrowing of cerebral arteries.

Dr. Eugene Ziskind provided electroencephalographic equipment for this study.

PYRETOTHERAPY IN OPHTHALMOPLEGIC MIGRAINE

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IN A PREVIOUS study of ophthalmoplegic migraine,[1] I reported two cases in the course of which the unexpected development of an incidental febrile state (typhoid and abscess of the arm, respectively) had a rapid curative effect. Previous therapeutic efforts had been unavailing. Stimulated by that fortunate accident, I used pyretotherapy in three other cases of ophthalmoplegic migraine, with very satisfactory results. In the first of these (Case 10[1]), in spite of interruption of the treatment, improvement has been maintained, and in the other two (Cases 14 and 15[1]) recovery was rapid and complete.

Five new cases of ophthalmoplegic migraine are reported in which pyretotherapy cured this pathologic state, which had shown not the slightest sign of improvement up to the time of fever therapy. The results obtained in these cases seem to confirm the efficacy of pyretotherapy in ophthalmoplegic migraine, so that the disease need no longer be considered beyond our therapeutic control.

REPORT OF CASES

CASE 1.[2]—Cats. A., a woman aged 25, had no history of migraine, either personal or hereditary, or of syphilis.

On March 15, 1948, without any apparent cause, she was seized with a violent pain on the right side of the head, which lasted three days. At the beginning of October the headache recurred and lasted eight days. On Oct. 20 she had a new attack of the headache, with vomiting. On Oct. 23 ptosis of the right eyelid appeared. On Nov. 11 the patient entered the hospital. The pain was generalized over the head but was especially severe in the right frontal area.

Examination on admission revealed ptosis and paralysis of the superior rectus, the internal rectus, and the inferior rectus on the right side. The iris on this side lay next the external palpebral commissure. The pupils were equal, and their reactions were normal. The optic disks were normal. The deep reflexes were normal. Sensibility was normal. Roentgenograms of the skull revealed nothing abnormal.

The urine was normal, as was the blood picture. The Wassermann and Kahn reactions were negative. Examination of the spinal fluid showed 330 mg. of protein per 1,000 cc. and 4 cells per cubic millimeter, with negative reactions in the Nonne-Apelt, Pandy, and Wassermann tests.

From the Department of Neurology of Evanghelismos Hospital.

1. Patrikios, J. S.: Ophthalmoplegic Migraine, Arch. Neurol. & Psychiat. **63**:902-917 (June) 1950.

2. This patient, observed prior to the time of my previous publication,[1] was not included in that report, the record having been mislaid in the archives of the department.

Pyretotherapy was begun, with injections of typhoid-paratyphoid A and B vaccine, as follows:

Dates	Degrees of Temperature
Nov. 18	39.0 C. (102.2 F.)
Nov. 22	39.2 C. (102.6 F.)
Nov. 26	40.0 C. (104.0 F.)
Nov. 30	39.0 C. (102.2 F.)
Dec. 3	39.3 C. (102.7 F.)
Dec. 10	39.8 C. (103.6 F.)

After the fall in temperature in the first attack of fever, the hemicrania became less intense and the ptosis slighter. With successive episodes, the pain diminished progressively, and the motility of the eyeball and eyelid increased day by day. When the patient was discharged, on Dec. 21, there was no trace of pain, and the motility of the eyelid and the eyeball was fully restored.

CASE 2.—Left., aged 46, had a history of measles at the age of 10 years and of pleurisy at the age of 15. There was no history of migraine, either personal or hereditary, or of syphilis. Early in May, 1949, headache began, becoming progressively intense and later being accompanied by nausea and vomiting and, finally, by diplopia. This state continued through May and then diminished in severity gradually up to the time of recovery, on June 15. After that the patient was in good health except for slight and rare headaches, of short duration.

In January, 1950, the headaches returned in violent form. They were localized to the right side of the head and face and were accompanied with nausea and a mild febrile reaction (37.3 C., or 99.2 F.). The condition continued to grow worse. On Jan. 17 she began to complain of diplopia on looking to the right. On Jan. 20 ptosis of the right eyelid appeared. On Jan. 30, when she entered the hospital, she was suffering from continuous violent right hemicrania, with complete ptosis of the right lid, paralysis of the right external rectus, and hyperesthesia of the right cheek.

The pupillary, deep, and plantar reflexes were normal. The optic disks and the visual fields were normal. X-ray studies of the skull revealed nothing abnormal.

The urine and blood were normal. The Wassermann and Kahn tests were negative; the blood sugar was 930 mg., and the blood urea 360 mg., per 1,000 cc. Examination of the spinal fluid revealed 200 mg. of protein per 1,000 cc. and negative Nonne-Apelt, Pandy, and Wassermann reactions. The cell count was 1 per cubic millimeter.

Her state was growing worse, and on Feb. 8 ophthalmologic examination showed complete ptosis and complete ophthalmoplegia on the right side. No movement of the eyeball was possible. The right pupil was larger than the left. The pupillary reactions were extremely slow and very limited.

Under these conditions, I advised pyretotherapy, which the patient was slow to accept.

On Feb. 16 the first injection of Dmelcos (Nicolle's antichancroidal) vaccine produced a temperature of only 38 C. (100.4 F.). However, the next day there was slight improvement in the headache, which subsided on the second day. On Feb. 19, with steady improvement in the headache, the eyelid could be raised slightly, and the eyeball moved outward and downward. The fever therapy was carried out as follows:

Feb. 21	38.2 C. (100.8 F.)
Feb. 25	38.0 C. (100.4 F.)
March 1	38.0 C. (100.4 F.)

At the end of these treatments the headache had disappeared; sensation over the cheek was normal, and the motility of the eyelid and eyeball was progressively increasing. Only very low temperatures having been obtained up to that time, I changed from use of the Dmelcos vaccine to that of typhoid-paratyphoid A and B vaccine, with the following results:

March 6	38.6 C. (101.5 F.)
March 12	39.2 C. (102.5 F.)
March 16	38.8 C. (101.8 F.)

At the end of these episodes the eyelid could be raised normally; the motility of the eyeball showed progressive improvement, but there was a deficit in the action of the superior rectus, the inferior rectus, the internal rectus, and the superior oblique, and in the pupillary reaction.

After two more fever bouts, on March 23 (38.6 C.) and March 30 (38.9 C., or 102 F.), all the movements of the eyeball became normal, but the reaction of the pupil was still slightly slow. The patient was discharged.

In April, 1951, when she returned, she said that she had had no more headaches, and that movements of the eyeball outward and inward were normal.

In this case, after the first appearance of the process, recovery was spontaneous in a month, and the condition was quiescent for seven months, after which it recurred in a more violent form, the ophthalmoplegia appearing eight days after the onset of the pain and becoming progressively complete. On the whole, the syndrome in this case was graver and more complete, and nine bouts of fever were necessary. Nevertheless, the recovery started with the first fever treatment, in spite of the slightness of the fever obtained.

CASE 3.—Calf., aged 42, had no history of migraine, either personal or hereditary. An attack of syphilis in 1937 had been adequately treated.

In January, 1951, after having worked in a snow storm, he was seized with a violent pain on the left side of the forehead and face. He was unable to sleep and suffered all night. In the morning paralysis of the left side of the face was obvious. This condition persisted for a month. At the beginning of March a tremor of the left eyelid appeared and became increasingly intense. On March 20, this slight trouble persisting, pain appeared in the left frontal area, with vomiting during the exacerbations. At the beginning of April the left eyeball became painful. Then the patient began to see double and the left eyelid to droop. The pain involved the cheek and the teeth of the upper jaw on the left side. By the end of April the attacks of vomiting had nearly ceased. The headache and the pain in the cheek were continuous and violent, and the ptosis of the left eyelid was then complete. On May 4, when the patient entered the hospital, examination revealed absolute ptosis of the left lid and complete ophthalmoplegia externa (left third, fourth, and sixth cranial nerves). The eyeball was motionless; the pupillary reactions were normal. The optic disk was normal. A slight hyperesthesia of the left cheek was noted. Deep and cutaneous reflexes were normal.

The blood urea was 210 mg., and the blood sugar 1,500 mg., per 1,000 cc. The blood count and blood formula were normal. Examination of the spinal fluid showed 330 mg. of protein per 1,000 cc., negative Nonne-Apelt, Wassermann, and Pandy reactions, and a cell count of 0.5 per cubic millimeter.

A roentgenogram of the skull revealed no abnormality.

Under the circumstances, I decided to induce fever by means of intravenous injections of typhoid-paratyphoid A and B vaccine. On May 13 the first febrile attack was induced, the temperature reaching 39.6 C. (103.3 F.). On May 18, after the second febrile attack, the temperature reached 39 C., and the next day the pain had subsided and the eyelid could be raised slightly. Since the patient was fatigued, the next febrile bout was postponed until May 24, when a temperature of 38.6 C. was reached. On May 29 a temperature of 39.6 C. and on June 3 a temperature of 40 C. were obtained.

The headache had long since disappeared; the eyelid could be moved normally, and the movements of the eyeball were extensive inward and outward, but much less extensive upward and downward. Diplopia persisted. Fever therapy was continued as follows:

June 8	39.6 C.
June 14	40.0 C.
June 20	39.2 C.
June 24	39.8 C.

The movements of the eye were reestablished to a normal degree.

When the patient left the hospital, on July 4, he considered that his recovery was complete. On examination in October he appeared very well except that he had twice felt a very slight frontal pain, which had lasted about half an hour.

In this case, again, the pathologic process of a grave ophthalmoplegia had been present for four months without modification at the time pyretotherapy was begun, and it was necessary to repeat the febrile episodes for reduction of the process. Nevertheless, recovery started with the first fever bout.

This case is interesting, also, from the pathogenic point of view. At the beginning the condition seemed to be a simple left facial paralysis, accompanied by violent neuralgia of the left side of the head and face, and its course toward recovery in a month seemed to corroborate such an interpretation. Things were not so simple, however. The subsequent course indicated that something unsuspected had begun to develop on the day of exposure to cold and that the immediate incident to appear was a prosopoplegic migraine; that, in spite of the clinical silence which succeeded the first incident, the pathologic process continued its activity, manifesting itself a month later in the form of a tremor of the eyelid, to be accompanied subsequently by true hemicrania with vomiting, and finally by ophthalmoplegia, the whole syndrome of ophthalmoplegic migraine organizing itself little by little during the four months following the provocative incident.

CASE 4.—Alf., a man aged 57, had no history of migraine, personal or hereditary, or of syphilis. In 1929 he had dengue fever. He was found to have diabetes a year prior to his admission. In April, 1951, he had colitis, with three or four stools a day. This state continued for 15 days, the patient continuing his work, when he was seized with pain on the left side of the head, involving the frontal area and the eye. Two days later, with the pain becoming more intense, ptosis of the left eyelid appeared. The patient could no longer sleep and had been obliged to give up his work.

The condition persisting during May, the patient entered the pathologic department on June 1. There the colitis was cured, and the diabetes brought under control, but the ophthalmoplegic migraine continued. On June 13 he entered the neurologic department, with the complaint of continuous violent pain, which prevented sleep.

Clinical examination showed complete ptosis of the left eyelid and slight paralysis of the internal and the superior rectus on the same side. The pupillary reflexes were normal. The optic disks were normal. The knee jerk and the Achilles reflex were suppressed (diabetes).

The blood count and blood formula were normal. The blood sugar measured 1,480 mg., and the blood urea 390 mg., per 1,000 cc. The Wassermann and Kahn reactions were negative. The urine contained no sugar; its specific gravity was 1.015.

Examination of the spinal fluid revealed 1,100 mg. of protein per 1,000 cc.; the Nonne-Apelt and Pandy tests were positive, and the Wassermann reaction was negative. The red cells were abundant, probably owing to injury to vessels during the spinal puncture.

X-ray examination of the skull revealed nothing abnormal.

On June 20 I induced the first febrile bout, obtaining a temperature of only 37.8 C. (100.4 F.). In spite of the low febrile reaction, there was a slight alleviation of the hemicrania the next day. On June 24 a second febrile bout was induced, and a temperature of 39.1 C. (102.4 F.) was obtained. The next day there was great improvement in the hemicrania, and the eyelid could be raised slightly. On June 29, in a third fever episode, the temperature reached 39.6 C. (103.3 F.). Improvement in the pain was greater, and the eyelid could be raised higher. On July 6 a temperature of 39 C. (102.2 F.) was obtained, and the eyelid could be raised normally. After two febrile episodes, on July 11 (39 C.) and July 18 (38 C., or 100.4 F.), all traces of pain disappeared, and the motility of the eyelid and the eyeball was practically normal.

The patient prolonged his stay in the hospital for the full control of his diabetes, and when he left, on Sept. 1, he was very well. Unfortunately, he did not consent to have a second examination of the spinal fluid, but we were convinced that the red cells revealed in the spinal fluid were due to a small hemorrhage produced by the puncture.

In this case, again, one of less violent and less complete ophthalmoplegia, the healing effect of the pyretotherapy was obvious with the first bout of fever, in spite of the slightness of the fever induced (37.8 C.) and the fact that the process had been present for two months before the treatment was begun.

This case is interesting as well from the pathogenic point of view. The migrainous process, almost immediately ophthalmoplegic, appeared on the 15th day of an attack of acute colitis, which had not been particularly severe. The ophthalmoplegic migraine had persisted without change after the colitis had been cleared, until pyretotherapy had been instituted to check it.

CASE 5.—Boul., a woman aged 38, had no history of migraine, either personal or hereditary.

On July 10, 1951, without evident cause, there was sudden appearance of headache on the right side. On July 14, the pain continuing, the right eyelid began to droop. On July 18, with the hemicrania persisting and the ptosis becoming more pronounced, the patient began to see double. On Aug. 1 she entered the hospital, with continuous right hemicrania.

Clinical examination revealed complete ptosis of the right eyelid. No single voluntary movement of the right eyeball was possible. The right pupil was large and did not react to light or in accommodation; the left pupil reacted normally. The optic disk was normal. The deep and cutaneous reflexes were normal.

The Wassermann and Kahn reactions of the blood were negative. The blood count and blood formula were normal. The blood sugar measured 970 mg., and the urea .250 mg., per 1,000 cc. The urine was normal. Examination of the spinal fluid revealed 330 mg. of protein per 1,000 cc., and the Nonne-Apelt and Pandy tests gave negative reactions. The cell count was 1 per cubic millimeter.

X-ray studies of the skull revealed nothing abnormal.

On Aug. 11 I induced the first febrile attack, the temperature reaching 38.2 C. (100.8 F.). On Aug. 16, in the second febrile attack, the temperature reached 38 C.; the severity of the headache was already lessened, and the motility of the ocular muscles was progressively increasing. On Aug. 21, in the third bout, the temperature reached 38.8 C. (101.8 F.). On Aug. 24 it was noted that the left eyelid rose very visibly. The movement of the eyeball downward approached the normal. There was the beginning of movement upward and inward. Pain was less severe. On Aug. 27, in the fourth bout, the temperature reached 39.8 C. (103.6 F.). The next day the eyelid could be raised almost completely. The movement of the eyeball downward was normal. Movements upward and inward had progressed. The eye could be moved slightly outward, and the pupil showed a beginning reaction to light. The hemicrania had disappeared.

On Sept. 1 the temperature reached 39.8 C.; on Sept. 6 it reached 39.6 C., and on Sept. 12 it was 39.4 C. (102.9 F.). At that time all movements of the eyeball had reached a normal degree except the one outward, which always presented some deficit, producing a slight diplopia. The pupillary inequality was always manifest; the pupillary reaction to light and in accommodation was present, but slow and incomplete. These reactions improved progressively day by day, although very slowly. Because of the persistence of a slight diplopia, at the request of the patient, I induced another febrile bout, with the temperature reaching 39.4 C. After this the pyretotherapy was discontinued. The improvement in the pupillary reaction and the diplopia continued spontaneously, but very slowly. Examination about the middle of November showed that the pupillary reactions were better, but not yet normal, and from time to time there was evident a slight diplopia at the extreme position of gaze to the right.

About the middle of December the pupillary inequality was hardly perceptible. The pupillary reactions were normal, but there was still a trace of diplopia in looking toward the right.

The peculiar feature in this case was bilateral horizontal nystagmus, of slight intensity, which was already present when the patient entered the hospital and had since diminished, but was still present at the time of the patient's discharge. This perhaps was to be explained by an extension of the pathologic process to the region of the nucleus of the sixth cranial nerve.

The ophthalmoplegia in this case being graver than in any of the others in this series, the number of fever bouts required was greater, but the result of the therapy has been maintained since the second febrile attack, despite the low temperature reached (38.2 C.).

COMMENT

What conclusions may be drawn from the present cases?

The first, of a pathologic nature, is in agreement with the conclusions in my previous paper and concerns the diversity of the precipitating factors in ophthalmologic migraine, when one happens to be discovered. In Case 3 the etiologic agent was the action of the cold; in Case 4, an associated colitis and diabetes. In this connection, it is interesting to note that in none of these cases was the process fully developed at its onset, but that it progressed slowly, little by little, as by a mechanism of "progressive maturation."

The second conclusion, of more practical character, concerns the efficacy of pyretotherapy in ophthalmoplegic migraine, so that one may now say that this syndrome, against which we have felt powerless, is no longer outside the range of therapeutic possibility.

These healing febrile bouts seem to release in the organism a therapeutic reaction, which continues to develop during the period after the fever, as when a healing process progressively opposes the pathologic process during its organization.

In my previous paper, I tried to explain the beneficial effect of the fever therapy as acting through a vasomotor mechanism. Such an explanation seems very simple. I believe that this beneficial action is to be explained by the mechanism of the general adaptation syndrome of Selye. The same mechanism is to be invoked to explain the development of the ophthalmoplegic migraine itself, this mechanism taking account of the diversity and nonspecificity of the causes producing this pathologic state.

CUTANEOUS PERCEPTION IN THE AGED

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AND
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NORMAL children 3 to 6 years of age [1] and normal adults [2] tested by the method of simultaneous tactile stimulation of the face and hand often fail to perceive or localize correctly one of the two stimuli. The perceptual error is usually in the hand stimulus. In children these errors persist during many tests and over an extended period. In normal adults the errors occur only during the initial tests and disappear on subsequent tests. However, there are some adults who make persistent errors. A review of a large series revealed that older people tended to make repeated errors in localizing the hand stimulus. For this reason, we analyzed the responses to stimulation of the face and hand in a group of adults of ages varying from 60 to 96 and compared them with those for normal adults under the age of 60.

SUBJECTS AND METHOD

The subjects consisted of 342 normal adults from 40 to 96 years of age (Table 1). The subjects under 60 years of age were nurses, hospital attendants, and friends, none of whom had

TABLE 1.—*Age Distribution of Subjects*

Age, Yr.	No. of Subjects
40-49	36
50-59	28
60-69	62
70-74	51
75-79	50
80-84	53
85-89	47
90-96	15

manifested disease of the nervous system. The subjects over 60 years of age were persons residing in old-age homes.[3] This group appeared to be a good sampling of the apparently "normal" older

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This work was aided, in part, by Grant #MH-139 with the United States Public Health Service.

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1. Fink, M., and Bender, M. B.: Perception of Simultaneous Stimuli in Normal Children, Neurology **3**:27, 1953.

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3. Dr. Frederic Zeman, Chief of Medical Service, Home for Aged and Infirm Hebrews, made these subjects available.

population. Most of the subjects were living in the old-age homes for social or economic reasons. They were able to care for themselves and were allowed to leave the home during the day. They were not considered to have "mental changes." Some of them had slight defects in memory, which many older people may exhibit. Subjects who showed gross mental changes, such as marked disorientation and confusion, were not included in this series. Old persons who showed signs of Parkinsonism or any other type of cerebral disease, such as hemiplegia, were also excluded from the study.

The method used in this investigation was the same as that employed in previous studies.[2] With the subject's eyes closed, the face and the dorsum of the hand were touched simultaneously by the examiner's fingers. The subject was asked to report what was felt and to localize the stimuli. If only one of the two stimuli was reported, he was questioned whether another was felt. Initially, 10 such face-hand tests were made in homolateral and heterologous relation and in random order.[4] Interspersed with the initial 10 tests was a single test in which both hands

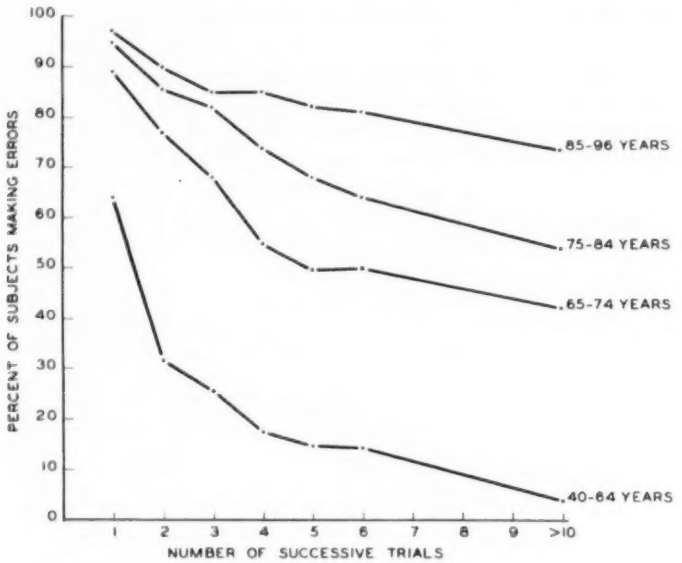

Chart 1.—Responses of normal aged subjects to the face-hand test.

were touched (homologous testing). After these initial 10 trials, tests of the thigh-foot combination were made in a similar manner and were followed by additional face-hand tests. Each subject had at least 18 tests.

RESULTS

Incidence of Errors.—Errors in perception of the two simultaneous stimuli were seen in all age groups, but their incidence and distribution during the series of tests varied with age. Thirty-six per cent of subjects 40 to 64 years of age made errors on the initial trial of the face-hand test, but nearly all these subjects correctly perceived both stimuli during the course of the first 10 trials and continued to localize them correctly on subsequent trials (Chart 1). In contrast to this, 96% of all subjects 65 to 96 years of age were incorrect on the initial trial, and 54%

4. In homolateral testing, body parts on the same side are touched, e. g., right cheek and right hand; in heterologous testing, asymmetric body parts on opposite sides are touched, e. g., right cheek and left hand; in homologous testing, symmetric body parts, e. g., right and left hands, are stimulated.

continued to make errors during the entire series of 10 tests (Chart 2). Many of these subjects perceived both stimuli correctly on some of the trials during the course of testing but made additional errors on later trials. The incidence of persistent errors increased with age. Thus, 42% of subjects 65 to 74 years of age, 54% of subjects 75 to 84 years of age, and 74% of subjects 85 to 96 years of age, gave incorrect responses throughout the series of tests. The accompanying graph illustrates this relation (Chart 1).

Pattern of Response.—The errors in perception consisted of failure to perceive one of the two stimuli (extinction) or mislocalization of one of the stimuli (displacement).[5] Extinction was commoner than displacement. Only 10% of the sub-

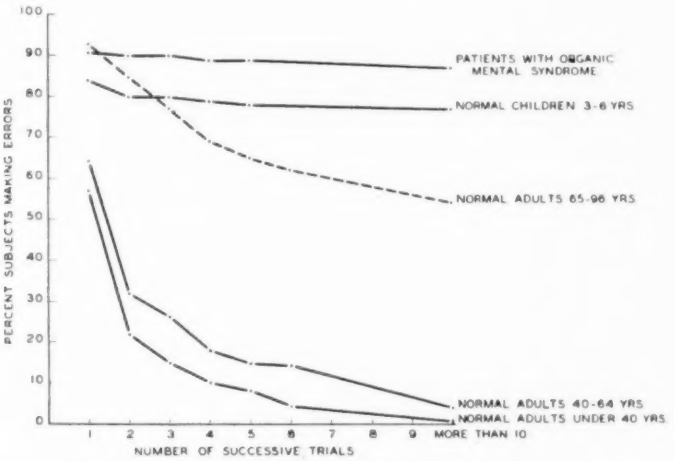

Chart 2.—Responses on the face-hand test with tactile stimuli.

TABLE 2.—*Pattern of Responses in 342 Normal Adults, Aged 40 to 96, to Multiple Simultaneous Tactile Tests*

Body Combination	Total No. of Tests	Total No. of Errors	Dominant Responses	
			Face	Hand
Face-hand	4,452	1,985	1,870	85
			Thigh	Foot
Thigh-foot	554	248	74	160

jects over 65 years of age showed more than three displacements during the entire series of tests. The displacements occurred oftenest in the direction of the dominant stimulus. Occasionally, they occurred across the midline of the body (allesthesia), but there were no instances of displacement into extrapersonal space (exosomesthesia).[6]

5. Bender, M. B.: Extinction and Precipitation of Cutaneous Sensations, Arch. Neurol. & Psychiat. **54**:1, 1945.

6. Shapiro, M. F.; Fink, M., and Bender, M. B.: Exosomesthesia or Displacement of Cutaneous Sensation into Extrapersonal Space, A. M. A. Arch. Neurol. & Psychiat. **68**:481-490, 1952.

These perceptual errors occurred in a characteristic pattern. In tests of face and hand the face stimulus was perceived correctly, while the hand stimulus was incorrectly perceived. In tests of the thigh and foot, incorrect responses were most frequent to stimuli over the thigh. Thus, the face was dominant to the hand and the foot dominant to the thigh (Table 2).

COMMENT

The present study of older people completes one aspect of an investigation of the entire normal population to tests of double simultaneous stimulation, or, more particularly, to the face-hand test. Normal adults over 65 years of age tend to resemble normal children in the incidence and pattern of perceptual errors (Chart 2). A large number of very young and very old subjects are incorrect on the initial trial of testing, and they persist in making errors during a series of many tests. This phenomenon is most pronounced in the youngest children and in the oldest adults. The incidence of such errors in both groups diminishes with changes in age

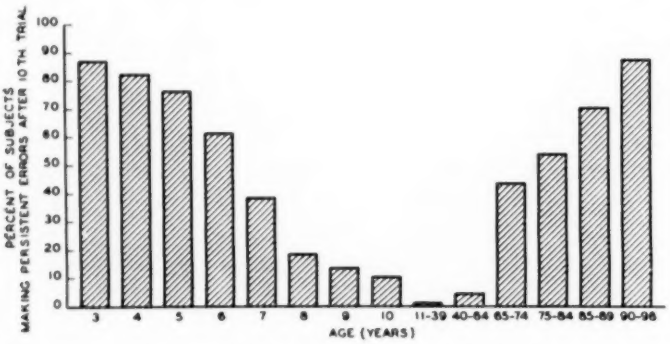

Chart 3.—Incidence of persistent errors on the face-hand test in normal subjects.

in a direction away from either extreme, i. e., toward the older child or the younger adult (Chart 3). The two groups are also similar in their pattern of response. In face-hand and thigh-foot tests perceptual errors are most frequent in the hand and thigh respectively. The face is dominant to the hand and the foot dominant to the thigh.

In contrast to the persistent errors manifested by normal children and very old persons are the responses of normal subjects 11 to 65 years of age.[2] This group shows a smaller incidence of incorrect responses on the first trial, and nearly all persons who do make initial errors correctly perceive both stimuli by the 10th trial and continue to do so during subsequent trials.

The observation that perception of simultaneous stimuli in the normal subject varies with age and is most "faulty" at the beginning and at the end of the life span is not surprising. This general phenomenon holds true for other measured functions of the nervous system, such as intellectual capacity and neuromuscular performance, both of which are not fully developed in the child and are not as efficient in the aged as in younger adults.

Persistent perceptual errors on simultaneous tactile tests not only occur in a majority of normal children and normal older adults, but also are observed in most patients manifesting an organic mental syndrome[7] due to permanent or transient cerebral dysfunctions produced by various structural or chemical alterations.[8] In fact, the high incidence of persistent perceptual errors in these psychotic patients, and not in normal adults, has led to the adoption of the face-hand test as a means of detecting the organic mental syndrome.[8a] From the foregoing observations it might be concluded that the occurrence of the same phenomena in many aged persons is most probably a reflection of structural alterations in the brain, mostly vascular in nature, which accompany the normal aging process. In other words, it is an involutionary change or a so-called physiologic change, which occurs with age. This is a situation which is analogous to the impairment of the sense of vibration one may find in the aged consequent to an arteriosclerotic process in the spinal cord[9] or to the increasing incidence of a Babinski sign in subjects over the age of 50 without other manifest symptoms of nerve dysfunction.[10] However, it must be emphasized that the changes which are found on double simultaneous stimulation in the so-called normal old adult are not nearly as prominent as in the younger patients with diffuse cerebral dysfunction.

SUMMARY

Tests of double simultaneous tactile stimulation, particularly the face-hand test, were performed on 342 normal adults of ages varying from 40 to 96.

Thirty-six per cent of subjects 40 to 65 years of age made perceptual errors on the initial test, but nearly all these correctly perceived both stimuli during subsequent trials.

The perceptual errors consisted of extinction or displacement of one of the two stimuli. This phenomenon occurred in a pattern in which the face was dominant to the hand and the foot dominant to the thigh.

Of the group 65 to 96 years of age, 96% showed errors on the initial trial, and 54% persisted in their errors after 10 trials of tests. The incidence of persistent errors in this group increased with increasing age.

This relation of age to persistent errors in the very old subjects is similar to that demonstrated in normal children under 6 years of age; the younger the child, the greater the incidence of persistent incorrect responses. Perception of double simultaneous stimuli in the normal subject is therefore most faulty at the beginning and the end of the life span, but the causes of the changes in each group must be different.

7. An organic mental syndrome consists of defects in orientation, memory, calculation, and general information characteristic of diffuse brain dysfunction.

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9. Pearson, G. H. J.: Effect of Age on Vibratory Sensibility, Arch. Neurol. & Psychiat. **20**:482, 1928.

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CEREBRAL LOCALIZATION AND THE CONTRIBUTIONS OF PSYCHOSURGERY AND SHOCK THERAPY

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SOME OF the newer psychiatric treatments have their root entirely in neurological thinking and were developed in part by neurologists. Therefore it seems in order to discuss the question of how much these treatments have contributed to the localization of psychotic manifestations. Psychosurgery has made obvious contributions to cerebral localization, since the areas of operation are more or less well defined. Shock therapy, in which the areas affected are not clearly defined, has been included in this study because some observations, especially some differences between manifestations in shock therapy and those in psychosurgery, seem to permit certain conclusions.

Psychosurgery started at a time when neurology was shifting from limiting itself to the study of individual areas of the brain to a greater emphasis on the functions of the brain as a whole. Recent knowledge suggests that localization of mental function in certain parts of the brain is still possible, but that we must think in terms of larger parts of the brain. The most important conclusion that has emerged from experience with the various psychosurgical methods is that the effect of these operations does not change with the particular area of the frontal lobe which is cut. It is, rather, the quantity of destroyed pathways that determines the intensity of mental changes, while no evidence has been found that any particular part of the frontal lobe has specific functions. When this quantitative principle is applied to the development of psychosurgery, it immediately appears that in the first case in which Burckhardt [1] operated, in 1890, an increasing reduction of symptoms occurred with each of the subsequent five operations. Moniz' [2] basic concept that bilateral destruction of frontal lobe fibers is a necessary premise for the desired clinical changes becomes questionable, since unilateral operations do not differ in the type of changes produced from bilateral operations, and may be therapeutically effective in cases of intractable pain and certain psychiatric conditions, although the clinical results as a whole are inadequate, and not lasting. Freeman and Watts [3] have

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Read at the Seventy-Seventh Annual Meeting of the American Neurological Association, Atlantic City, N. J., May 10, 1952.

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3. Freeman, W., and Watts, J. W.: Psychosurgery in the Treatment of Mental Disorders and Intractable Pain, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1950.

shown that their three methods, i. e., the standard lobotomy at the level of the coronal suture, the "radical" method, with a more extensive posterior cut, and an anterior, "minimal," operation, differ only in degree as far as therapeutic results and undesirable personality changes are concerned. The numerous variations of partial lobotomies and other less extensive operations differ from the original lobotomy in degree but not in the type of clinical effects. A reduction in personality changes with still adequate clinical results can be obtained not only by moving the cut forward, toward the frontal pole, where fewer fibers are met (precoronal lobotomy, or McKissock's [4] rostral leucotomy), but equally by limiting the lobotomy to both medial or both lateral halves of the frontal lobes. The least effect is obtained with the transorbital approach, of which, at least in our experience, the original method was inadequate, and only with the additional deep frontal cut, as devised by Freeman [5] did results become slightly more satisfactory. The best evidence against the localization of a specific function in any particular part of the frontal lobe was brought by the work with topectomies, as demonstrated by Pool [6] on the basis of his extensive work with selected partial ablations of the frontal cortex (Mettler [7]). Evidence similar to that from these cortical operations was presented by Scoville [8] in his undercutting of three different areas of the frontal lobe, which had largely identical psychiatric results. This constantly increasing clinical evidence was preceded by A. Meyer's [9] anatomical studies on lobotomies, which showed identical clinical results after quite different cuts that produced different areas of degeneration in the dorsomedial nucleus of the thalamus. The question arises how far any specific function can be attributed to the frontal lobe, in contrast to other cortical areas. Present evidence of psychosurgery on the temporal, parietal, and occipital lobe is too scanty to permit conclusions.

Some negative findings in work with psychosurgery are startling in the light of previous concepts, and they require further study. One such observation was the apparent absence of focal symptoms following lobotomies of parietal and other areas, where focal symptoms were to be anticipated. Another observation of interest, made in the Columbia Greystone project,[7] was the failure of ablation of the left lower frontal gyrus to produce aphasic symptoms. It is a challenging question why psychosurgery sometimes fails to elicit focal signs in areas where circumscribed pathological conditions, such as tumors and vascular lesions, usually give well-known clinical syndromes.

Another important contribution of the work in psychosurgery is the observation that the basic intellectual and emotional functions of man are not limited to the frontal lobe, as was thought by many clinicians in the past. With small operative lesions of the frontal lobe these functions are basically unchanged; with more exten-

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sive lesions they are impaired in some ways, but they are never completely lost, or even severely impaired. It can be concluded, therefore, that they have a wide representation in the brain and that the frontal lobe has only a limited part in their representation.

Experience with the psychopathology of all brain lesions has demonstrated that it is necessary to differentiate clearly between focal and general symptoms. The final changes in psychosurgery—the therapeutically valuable as well as the undesirable effects—must be conceived of as focal manifestations; but, like most operations on the brain, psychosurgical procedures are also followed by general symptoms. These symptoms are mostly transitory, appearing during the first postoperative period, and cover the later-appearing focal effects of the operation. They persist longer after extensive operations, may be very short after restricted operations, such as topectomy, and are negligible after the transorbital lobotomy, which is the least extensive cut in the frontal lobes. They do not differ from the psychopathological findings in numerous cerebral disorders and consist in clouding of consciousness with organic reactions, often described as the "amnestic syndrome," and always accompanied with emotional changes as well. Their almost complete absence in some of the less extensive operations on the frontal lobe again refutes previous concepts of the importance of the frontal lobe in mental function. It should also be pointed out that consciousness, as a rule, is not affected by any of the frontal-lobe procedures used in psychosurgery. Operations performed with the patient under local anesthesia have clearly shown that consciousness is not related to the normal functioning of the frontal lobes, or, for that matter, of any cortical area. The most extensive cuts in both frontal lobes can be performed without loss or impairment of consciousness. This is strong support for the view that unconsciousness occurs only when the functioning of deeper parts of the brain is interfered with. This assumption has been made before on the basis of clinical evidence and is fully upheld by the large material available from psychosurgical operations.

The essential difference between psychosurgery and shock treatment in connection with the questions under discussion is the fact that shock therapy affects the entire brain. This is true not only of insulin shock treatment but also of convulsive therapy, although it can be assumed that the trigger point of a convulsion is a well-circumscribed, though still unknown, area of the brain. It is not surprising, therefore, that experience with these treatments has contributed little to problems of cerebral localization. It will be attempted, nevertheless, to discuss several points which seem to be of interest for questions of localization. If the principle of focal and general symptoms is applied to electric shock treatment, the organic reaction, with memory impairment and emotional blunting, is easily comparable to the general symptoms of the immediate postoperative period of frontal lobe surgery. The patient "forgets" his symptoms, but this effect is quite unrelated to the final outcome, either in psychosurgery or in shock therapy. The general symptoms in shock treatment can be explained as general cerebral dysfunction, which is evidenced in electroencephalographic and psychological disturbances and is quite similar to what is seen in repeated epileptic convulsions. Their chief clinical manifestations are impairment of memory and emotional blurring, but the patient may present a great variety of organic reactions, such as are seen in many instances of interference with brain function. Such organic reactions, ranging from a simple amnestic syndrome over delirium-like syndromes to severe dementia, are not accompanied with any focal

or generalized anatomical changes in the brain. Even when severe, they are of short duration; and only after they have cleared up do the actual therapeutic effects achieved by the shock therapy become manifest. Lasting side-effects in the sense of personality damage are never observed after this form of therapy, and it is in accordance with the experience of organic "symptomatic" psychoses of any other origin that even a severe dementia invariably clears up completely within a short time.

Of focal changes observed in shock therapy, two types appear: the psychopathological changes, in the sense of disappearance of psychotic symptoms, and changes in certain physical symptoms, which parallel the mental changes. The physical symptoms of the illness consist in disturbances primarily in weight, sleep, and menstruation, all of which point to a diencephalic localization. Simultaneously with, and even preceding, the disappearance of psychotic symptoms in therapeutically responsive patients are gain in weight, return of normal sleep, and, somewhat later, disappearance of menstrual disturbances. The reversal of psychotic symptoms which takes place simultaneously with these diencephalic changes raises the question of an identical localization of the two sets of symptoms. It has been demonstrated in various neurological diseases, particularly brain tumors, and in experiments of stimulation of these areas during operation (Foerster and Gagel [10]) that the hypothalamus and midbrain are somehow related to manic-depressive and schizophreniform manifestations. In the French literature the localization of psychoses in the diencephalon and the focal effect of electroconvulsive therapy on this area (Delay [11]) have been emphasized. Certain obvious differences between favorable shock results and the outcome of psychosurgical operations seem to support such localization of mental symptoms in these deeper parts of the brain. The main difference is the persistence of some psychotic symptoms, such as delusions and hallucinations, in the majority of psychosurgical cases, even when the outcome is favorable, and only the reduction of anxiety connected with them changes the impact of these symptoms on the patient. This is contrary to the experience that when shock treatment is successful delusions and hallucinations disappear. In unsuccessfully treated patients they may also disappear temporarily, but they are obscured only by the general symptoms of memory loss, etc. When, within a week, these general symptoms disappear, however, the delusions and hallucinations reappear. If they do, the entire psychotic picture returns. This is quite contrary to the experience in psychosurgery, in which the patient shows improvement in spite of the reappearance of such symptoms. This difference between the clinical effect of psychosurgery and that of shock therapy suggests the following hypothesis: In psychosurgery the focus of the lesion set by the surgeon is known to be in the frontal lobes. If the psychotic manifestations as such remain uninfluenced by an interruption of pathways at this level, it is likely that those manifestations originate in deeper parts of the brain. Present evidence seems to indicate that such symptoms as delusions and hallucinations also do not disapper in operations on the temporal lobe. Their disappearance after favorable shock treatment, on the other hand, suggests that shock therapy affects areas of the

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brain which are below the frontothalamic and temporothalamic pathways sectioned in psychosurgery. The simultaneous vegetative changes in shock therapy point to the diencephalon as a possible point of origin for the psychotic syndromes and the possibility of their cure with a treatment which affects this area.

Reports on neurological observations in shock therapy are numerous and have been surveyed elsewhere,[12] but they have contributed little to knowledge of brain function. In insulin shock treatment attempts were made to localize the various clinical observations during hypoglycemia in terms of successive loss of function of various parts of the brain. In convulsive therapy similar observations were made during the postconvulsive state. Such attempts are interesting but do not promise additional information regarding cerebral localization. Similarly, it must be admitted that the attempts to localize convulsive phenomena have been disappointing. Focal stimulation through the unopened skull has been tried but can never reach the importance of focal stimulation of the brain during operation. Studies on convulsive threshold and other observations have yielded interesting information but have not contributed to localization. The only exception is perhaps the observation that the clonic phase of a convulsion can be suppressed by continued flow of the stimulating current; if it is assumed that such stimulation interferes with cortical function, this observation would support the theory that the clonic movements represent a cortical phenomenon of returning brain function which is suppressed by the disrupting effect of continued stimulation. However, animal experiments may clarify such problems equally well. This is not true for possible clues in connection with the cerebral localization of psychopathological manifestations. Here, investigations on animals can give only questionable information, interesting and thought-provoking as such studies may be.

The wealth of information given us by the various somatic treatments of psychiatric patients has, thus far, taught us but little about the localization of psychopathological manifestations. Yet this approach appears to be promising. It is true that the few deductions from clinical experience discussed in this paper are in part highly hypothetical. Other uses, such as application of the quantitative principle to the function of the frontal lobe, represent obvious contributions to our knowledge of cerebral function. Contrary to conclusions in the older literature drawn from isolated cases of injury, brain tumors, etc., recent considerations can be based on an enormous number of observations made on human material treated in various ways. In the light of such a wealth of new information, it is felt that, in spite of previous disappointment, the neurological approach to the cerebral localization of psychiatric manifestations should be taken up again.

115 E. 82d St., New York (28).

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GRANULOMATOUS ANGIITIS OF THE MENINGES IN SARCOIDOSIS

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ALTHOUGH involvement of cranial and peripheral nerves by sarcoidosis is well recognized,[1] sarcoidosis affecting the central nervous system and meninges is rare. From a review of the literature, there appear to be only 21 cases in which such a diagnosis was substantiated at necropsy and 4 cases in which the diagnosis was confirmed, by surgical biopsy. In many of the reports few or no clinical data are given, and the pathological studies are meager. Since sarcoidosis is a disease, or a group of diseases, of unknown etiology,[2] it is best recognized by its clinicopathological features.

Involvement of the nervous sytem by sarcoidosis has been critically discussed in several papers in the last decade,[3] and there is ample evidence both from clinical and from autopsy data that the brain, spinal cord, optic chiasm, meninges, and pituitary gland may be involved. Involvement of the central nervous system may be the cause of sudden death.[4]

The case to be reported is of unusual interest, for two principal reasons. First, the clinical state was that of rapidly fatal development of increased intracranial pressure simulating an intracranial space-occupying lesion. Second, the histological

From the Neurological Unit and the Mallory Institute of Pathology, Boston City Hospital.

1. Colover, J.: Sarcoidosis with Involvement of the Nervous System, Brain **71**:451-475, 1948.

2. (*a*) Fisher, A. M.: Some Clinical and Pathological Features Observed in Sarcoidosis, Tr. Am. Clin. & Climatol. A. **59**:58-74, 1947. (*b*) Jacques, W. E.: Sarcoidosis: A Review and a Proposed Etiologic Concept, A. M. A. Arch. Path. **53**:558-592, 1952.

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4. (*a*) Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease, J. A. M. A. **117**:1321-1327, 1941. (*b*) Longcope, W. T., and Freiman, D. G.: A Study of Sarcoidosis Based on a Combined Investigation of 160 Cases, Including 30 Autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital, Medicine **31**:1-132, 1952.

changes in the nervous system were those of a granulomatous angiitis and periangiitis confined to the leptomeninges, of an unusual type. An analysis of the symptoms in this case, together with a review of the few reported instances of sarcoidosis of the central nervous system studied pathologically, permits certain conclusions concerning the natural course of this rare disorder.

REPORT OF A CASE

G. C., a machinist aged 51, entered the Boston City Hospital complaining of severe headache of 10 days' duration and anorexia of two days' duration. The headache increased three days before entry, and he became lethargic and confused. The day prior to admission his physician found him afebrile, with normal pulse and blood pressure.

The patient had complained of "arthritis" for eight years, with intermittent swelling of the fingers, for which he took salicylates. He had taken 30 tablets (9 gm.) of acetylsalicylic acid and 2 grains (130 mg.) of codeine daily for three days before admission to relieve his headache.

Physical examination showed that the pulse was slightly irregular, with a rate of 48 per minute. The temperature was 101 F., the respiration rate 10 per minute, and the blood pressure 150/80.

The patient was lethargic and disoriented; he complained of headache and vomited frequently. The neck was supple. There was no adenopathy. The chest was emphysematous, with rales at the base of both lungs. The heart was not enlarged; a Grade-3 systolic murmur was heard at the apex. The abdominal organs were not palpable.

The pupils were constricted but reacted to light. The visual fields could not be tested. The fundi were normal. Examination of the cranial nerves showed no abnormality. There was no motor weakness. Bilateral grasping and reflex sucking were present. The deep reflexes were active and equal on the two sides, and the plantar reflexes were of flexor type. Painful stimulation produced withdrawal of all four extremities.

The white blood cell count was 11,000 per cubic millimeter, with 76% polymorphonuclear leucocytes and no eosinophiles. The corrected erythrocyte sedimentation rate was 30 mm. (Wintrobe). The hematocrit reading was 43. The thymol turbidity was 8 units. The serum nonprotein nitrogen was 26 mg. per 100 cc.; the CO_2-combining power, 51 vol. %; the chlorides, 93 mEq. per liter, and the fasting blood sugar, 125 mg. per 100 cc. The urine had a specific gravity of 1.020 and contained no sugar, albumin, or formed sediment. A roentgenogram of the chest showed patchy and linear densities at the bases of both lungs, emphysema, and elevation of the right side of the diaphragm. The heart was prominent transversely. A roentgenogram of the skull showed no abnormality. An electrocardiogram demonstrated a shifting auricular pacemaker with occasional auriculoventricular, or nodal, rhythm. Lumbar puncture on the first hospital day showed an initial pressure of 350 mm. of water, with a final pressure of 100 mm. after 15 cc. of clear, colorless fluid was withdrawn. The fluid contained 10 lymphocytes and 29 red blood cells per cubic millimeter. The Pandy test gave a strongly positive reaction for globulin; the total protein measured 103 mg., the sugar 89 mg., and the chlorides 812 mg., per 100 cc. The cerebrospinal fluid gave a negative reaction to the Hinton test, and the colloidal gold curve was 5433332221. Culture of the cerebrospinal fluid was sterile on two occasions. The electroencephalogram was grossly abnormal, with diffuse delta activity bilaterally, that on the right being slightly more pronounced.

The patient was treated with parenteral administration of fluids and intramuscular injection of aqueous penicillin, 100,000 units every four hours. His condition continued to deteriorate, and he became more confused and stuporous. On the fifth hospital day, papilledema developed bilaterally, and plantar reflexes became extensor.

Repeated blood cell counts did not reveal eosinophilia, and blood chemistry studies showed nothing remarkable except a gradual rise in the blood nonprotein nitrogen to 53 mg. per 100 cc.

Two further lumbar punctures were performed. On the second hospital day, the initial pressure was 450 mm. and the fluid was slightly xanthochromic, with 10 lymphocytes and 20 red blood cells per cubic millimeter. The Pandy test was positive for globulin, and the total protein was 80 mg. per 100 cc. The chlorides were 674 mg. per 100 cc. On the fifth hospital day, the cerebrospinal fluid pressure was over 500 mm. of water, and fluid was xanthochromic, the Pandy reaction was positive, and the total protein was 215 mg. per 100 cc.

On the fifth hospital day bitemporal trephinations were made in order to exclude the possibility of a subdural or an epidural space-occupying mass. The dura and the underlying portion of the brain were extremely tense. A right posterior parietal craniotomy was performed. The right tentorial edge was approached with difficulty because of cerebral edema. The tentorial edge was incised, but after the procedure the brain herniated through the opening in the parietal bone and the dura could not be closed. Plastic repair of the dura was made with nylon mesh.

Left sixth nerve paralysis developed after operation, and the patient died 24 hours later.

Summary.—A man aged 51 with a history of arthritis of the hands for eight years had onset of severe headache and anorexia. Examination revealed that he was febrile, lethargic, and disoriented. Rales were heard at the bases of both lungs. There was automatic motor activity in the form of reflex grasping and sucking.

Laboratory examinations revealed increased thymol turbidity, increased sedimentation rate, and patchy densities in the lung on roentgenographic examination. The cerebrospinal fluid was under increased pressure and showed an elevated protein content with pleocytosis.

Fig. 1.—Surface of frontoparietal cortex. The pial vessels are intensely congested, and numerous round white granulomata are seen along the course of small pial vessels.

He became stuporous; papilledema and extensor plantar reflexes developed, and death followed surgical intervention.

Necropsy.—Gross Examination: Numerous small granular red lesions were present in the skin overlying the right elbow; they were not removed for histological examination. There were surgical incisions, one each side of the scalp, which had been closed with silk sutures.

The lungs adhered partially to the pleural cavity by fibrous strands. The right lung weighed 900 gm., and the left, 700 gm. The apices and bases of the lungs appeared rubbery on palpation. The bases were red-brown, with numerous small white patches. The hilar nodes were enlarged, and several presented a yellow color on section.

The heart was enlarged, weighing 520 gm. There was relative hypertrophy of the wall of the right ventricle (0.6 cm.). The wall of the left ventricle averaged 1.5 cm. in thickness. There was moderate atherosclerosis but no occlusion of the coronary arteries.

The brain weighed 1,550 gm. There was herniation of the brain through the operative defect in the right parietotemporal region of the skull. The brain was swollen generally and partially necrotic at the point of herniation. The right tentorial edge had been incised.

The brain was reexamined after fixation in 10% formalin. The dural sinuses were patent. There was generalized swelling of the brain, with widening of gyri and narrowing of sulci. The swelling appeared maximal over both convexities, where the sulcal markings were partially obliterated. A small amount of fresh blood was diffused throughout the subarachnoid space. The pial vessels were intensely congested and unusually prominent. Along the course of many of the smaller vessels round white miliary lesions were scattered, measuring 0.2 to 0.5 cm. in diameter (Fig. 1). These were surrounded by a zone of brown hemorrhagic exudate. No purulent exudate was observed in the subarachnoid space.

There were a small groove on the left uncinate gyrus and a bilateral cerebellar cone. Coronal section revealed marked congestion of the subcortical white matter. The ventricles were small and not displaced. The ependyma was not unusual.

The carotid arteries in the neck were found to be patent. The major cerebral vessels were dissected and found to be of normal appearance.

The cervical portion of the spinal cord and its meninges showed no abnormality.

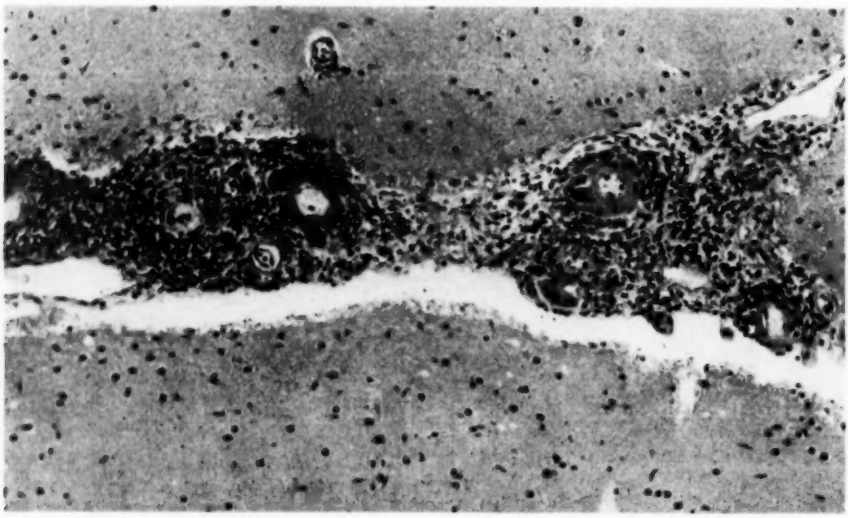

Fig. 2.—Perivascular granuloma in the pia-arachnoid of the cerebellum. Hematoxylin-eosin stain; × 100.

Microscopic Study.—Lungs: Sections of all lobes of the lungs showed numerous focal granulomata (Fig. 3*A*). These granulomata were similar in appearance and were confined to the alveolar septa and peribronchial tissues. Frequently they were perivascular and adventitial, only rarely involving the media (Fig. 3*B*). They consisted of epithelioid histiocytes and multinucleated giant cells of the Langhans type, which frequently contained asteroid bodies. No Schaumann bodies were noted. Plasma cells and lymphocytes were also present in small numbers. These granulomata showed varying degrees of fibrosis, but no caseation or infarct necrosis was present. No acid-fast bacilli were found.

Liver: A solitary fibrosed granuloma was found in a portal space (Fig. 4*B*).

Lymph Nodes: Numerous lymph nodes showed granulomata similar to those in the lung.

Kidneys: A few granulomata were found (Fig. 4*A*).

Other Organs: No granulomata were found, either grossly or microscopically, in the pituitary gland, spleen, heart, adrenal gland, bone marrow, skeletal muscle, peripheral nerve, testis, bladder, prostate, stomach, or pancreas.

Central Nervous System: Representative blocks of the frontal, temporal, parietal, and occipital cortex; the basal ganglia; the brain stem; the cerebellum, and the cervical portion of

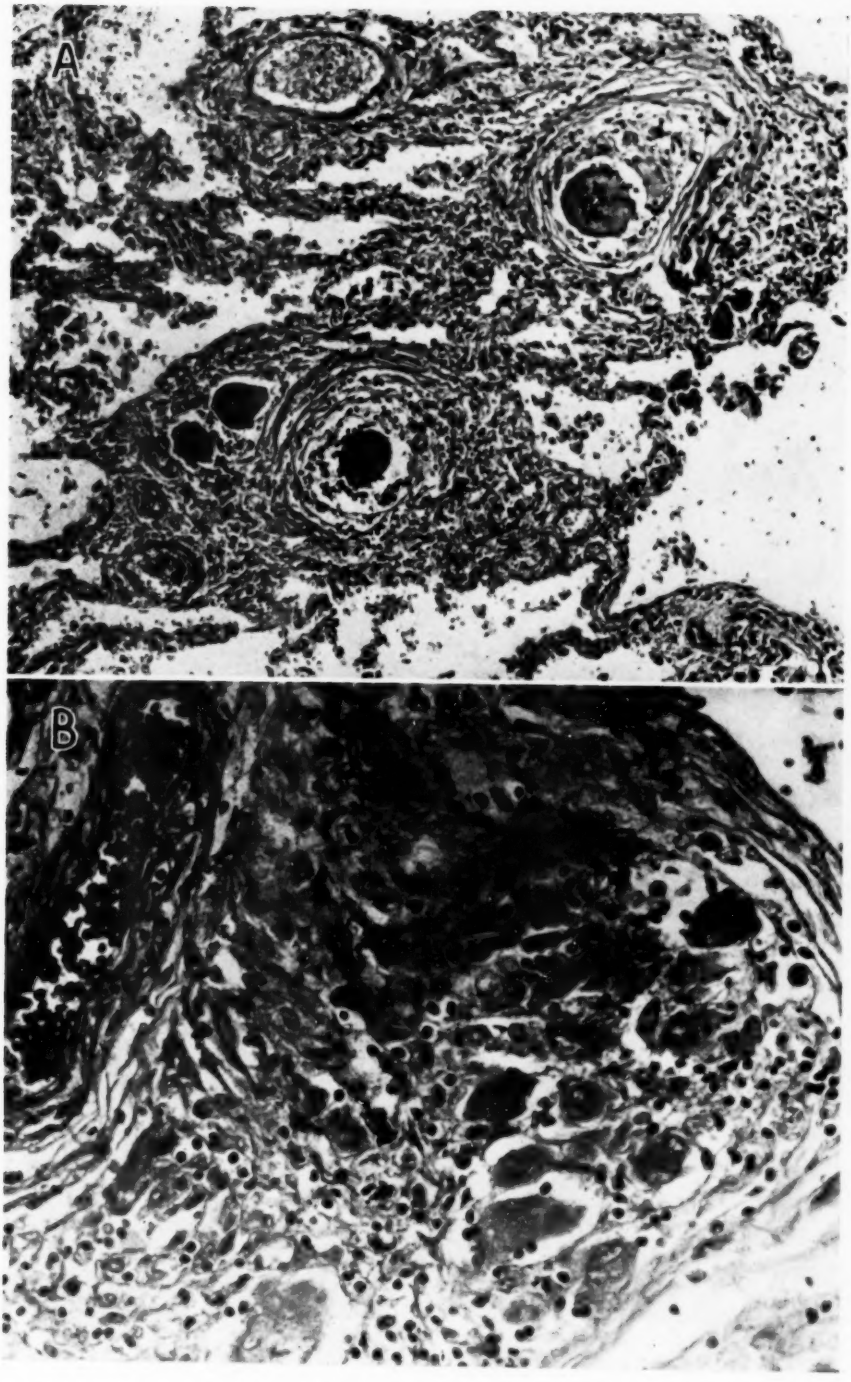

Fig. 3.—*A*, granuloma in lung. Hematoxylin-eosin stain; × 250. *B*, perivascular granuloma in lung. Hematoxylin-eosin stain; × 450.

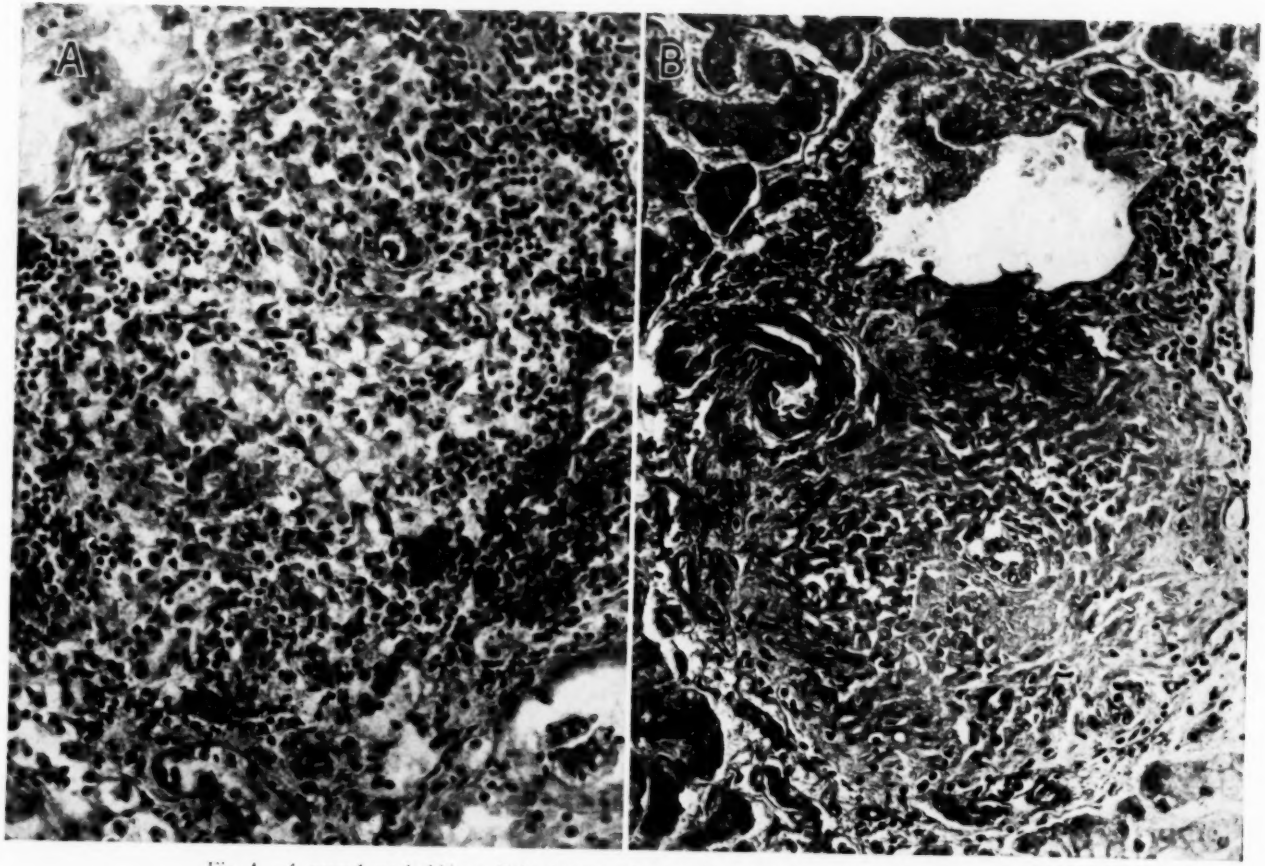

Fig. 4.—*A*, granuloma in kidney. *B*, healed granuloma in liver. Hematoxylin-eosin stain; × 375.

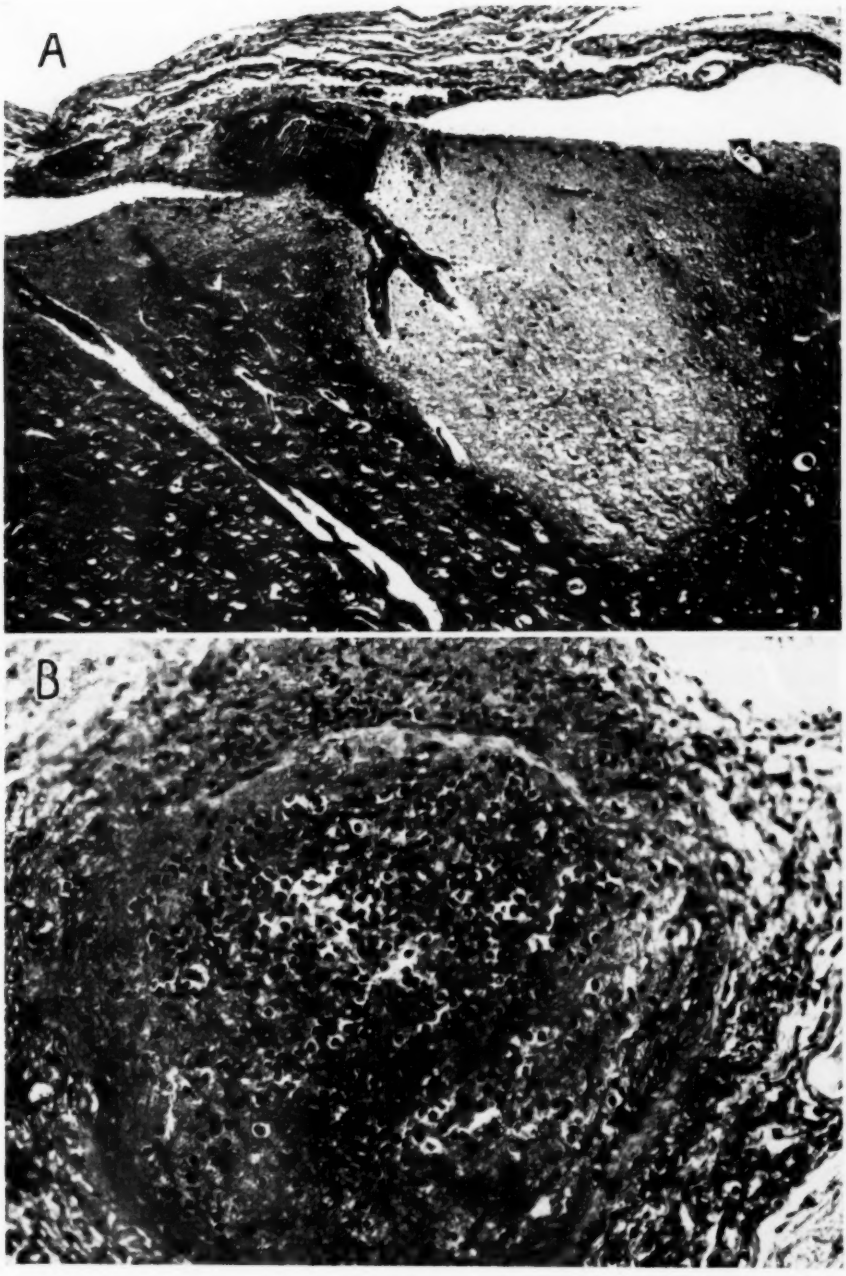

Fig. 5.—*A*, leptomeninges, showing occluded vessel with infarct necrosis in underlying brain. Verhoeff stain; × about 40. *B*, pial arteriole, showing involvement of all layers of the vessel wall. Hematoxylin-eosin stain; × 375.

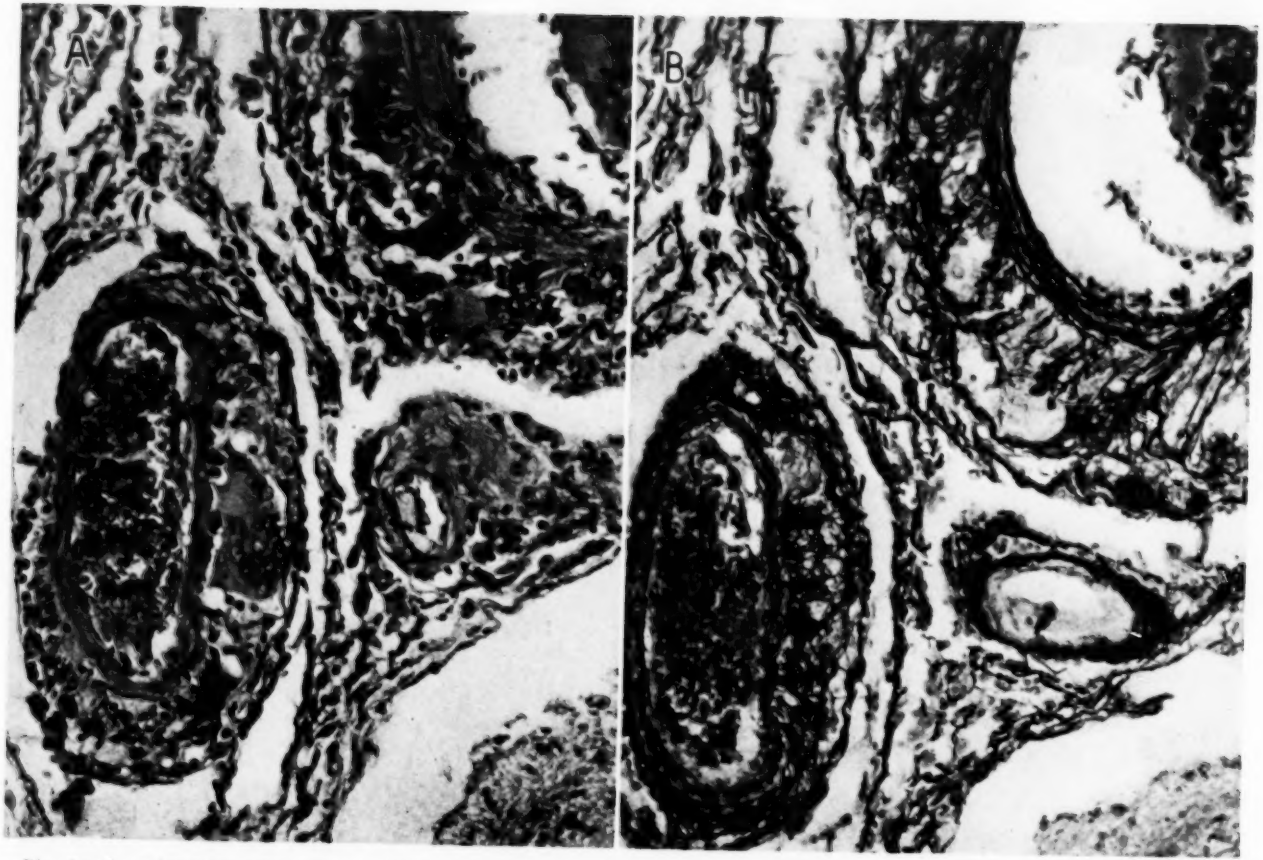

Fig. 6.—*A*, perivascular granulomata in parietal leptomeninges. Hematoxylin-eosin stain; × 375. *B*, proliferation of reticulum in adventitia (compare Fig. 6*A*). Reticulum stain; × 375.

the spinal cord were embedded in celloidin and stained with hematoxylin and eosin, Mallory's phosphotungstic-acid hematoxylin, and Loyez' method for myelin. Several blocks of the cortex and meninges were embedded in paraffin; sections were cut at 8 μ and stained by the Ziehl-Nielsen method for acid-fast organisms, the periodic-acid-Schiff method for fungi, the Giemsa method, phloxin and methylene blue, a reticulum stain, the Verhoeff elastic-tissue stain, and hematoxylin and eosin.

The leptomeninges showed a striking abnormality. Around both meningeal arteries and veins were numerous granulomata of the same general character as those seen in the lung (Fig. 2). These granulomata were in the perivascular spaces and in the adventitia and, more frequently than in the lung, extended into the media. Several small arterioles showed acute necrosis of all layers and recent thrombosis (Fig. 5*A*). The area of cortex supplied by such an occluded vessel showed recent infarction, with immigration of polymorphonuclear leucocytes and edema (Fig. 5*B*).

The perivascular granulomata were frequently found to follow the Virchow-Robin spaces deep into the cortex. No granulomata were observed in the cerebral substance, and there was no involvement of the white matter, basal nuclei, or ependyma.

Numerous perivascular granulomata were scattered through the subarachnoid space overlying the cerebellar folia, but the meninges of the brain stem and spinal cord were not affected.

Prolonged search revealed no acid-fast organisms. Specific stains showed a marked proliferation of reticulum both in the adventitia of the affected vessels and in the exudate surrounding them. There was no destruction of reticulum (Fig. 6*A* and *B*). Staining with the periodic acid-Schiff technique revealed no fungi. No inclusion bodies were evident. Stains for elastic tissue confirmed the structural involvement of the vessels by the granulomata. The elastica and media were not affected except in rare instances in which the entire wall of the small artery was undergoing acute necrosis.

The entire cortex showed patchy areas of acute infarction. In these areas the nerve cells appeared eosinophilic and swollen, and the nuclei were frequently displaced. Some polymorphonuclear neutrophiles emerged from the vessels and entered the infarcted tissue. The media of vessels showed no caseation or fibrinoid necrosis.

COMMENT

The diagnosis of sarcoidosis in the present case was made only after microscopic examination. It is an addition to the majority of reported cases of sarcoidosis of the central nervous system in which such a possibility was not given due clinical consideration as a cause of symptoms. Indeed, the number of cases are few in which the diagnosis of sarcoidosis of the central nervous system was entertained prior to operation or ante mortem, and usually attention has been called to this possibility by the more obvious features of generalized sarcoidosis, such as uveoparotid fever, lupus pernio (Boeck's sarcoid), or characteristic roentgenographic lesions of the lung or bone. In the present case insufficient attention was paid to the history of intermittent swelling of the hands, the pulmonary infiltrations, and the increased sedimentation rate and thymol turbidity. The dramatic signs of cerebral disorder, the increased intracranial pressure, and the meningeal reaction overshadowed the systemic disorder.

A review of the literature pertaining to sarcoidosis of the central nervous system allows some formulation of the usual evolution of this disorder, so that even in the absence of characteristic lesions of the skin and viscera one may conclude that there are clinical situations in which such a diagnosis should be entertained.

Pathologically, the lesions are of two sorts. The commoner variety is diffuse, a granulomatous leptomeningitis, occurring especially at the base of the brain in the region of the infundibulum, pituitary, and floor of the third ventricle. This type

Summary of Documented Cases of Intracranial Sarcoid, Proved at Autopsy or Operation

Author	Age, Yr.	Sex	Clinical Evidence of Sarcoid Elsewhere	Central Nervous System Manifestations	Cerebrospinal Fluid	Intracranial Pathological Findings
Strasmann [5a]	37	M	Facial lupus without caseation, 10 yr.	Headache, optic atrophy bitemporal hemianopsia, 1 yr.	.....	Granulomata at base, involving optic nerves and chiasm
Simons and Merkel [5b]	24	F	Lupus pernio, splenomegaly, adenopathy, 2½ yr.	Headache, vomiting, polydipsia, cranial nerve paralyses, extensor plantar responses, 6 wk.	.....	Granulomata of meninges, ependyma, optic nerves, and chiasm, 5th and 7th cranial nerves
Lenartowicz and Rothfeld [5c]	17	F	Skin lesions of face and body; osteitis cystica multiplex of hands and feet, 2+ yr.	Headache, papilledema, optic atrophy, exophthalmos, pyramidal signs, convulsions, 2 yr.	Increased protein	Massive leptomeningeal granulomata; compression of optic nerves and chiasm; infiltration of orbital surface of frontal lobes
Naumann [5d]	3/12	F	Retinal infiltrations; skin nodules, 5 wk.	Meningeal irritation, fever, convulsions, 5 wk.	Increased pressure and protein; pleocytosis	Leptomeningeal granulomata; infiltration of pons and cerebellum; dural and tentorial granulomata; hydrocephalus
Erickson, Odom, and Stern [5a]	31	M	Nodule on lip, 1 yr.	Vomiting, papilledema, mental dulness, convulsions, tinnitus, 8 mo.	Increased pressure and protein; pleocytosis	Granulomata of meninges and ependyma; infiltration of pons and cerebellum; hydrocephalus
Zollinger and von Meyenburg [5f]	21	M	.....	"Atypical multiple sclerosis" with headache, nystagmus, pyramidal and cerebellar signs, 1 yr.	Increased protein; pleocytosis	Leptomeningeal granulomata; widespread focal granulomata in brain
Zollinger [5g]	78	F	.....	"Recurring and remitting paralyses," 3 mo.	.....	Grossly normal; leptomeningeal granulomata seen microscopically

Zahn and Weber [5b]						
Case 1	40	M	.....	Lethargy, headache, stiff neck, 2 yr.	Increased protein; low sugar; low chlorides	Granulomata of meninges, ependyma; hydrocephalus
Case 2	27	M	.....	Lethargy, headache, stiff neck, 2 yr.	Increased protein; low sugar; pleocytosis	Granulomata of meninges and ependyma; hydrocephalus
Everts [51]	27	M	Proved sarcoid of adenoid (biopsy); hilar mass on chest x-ray, 1 yr.	Headache, diplopia, right homonymous hemianopsia, right hemiparesis, papilledema, convulsions, 1 yr.	Increased protein	* Circumscribed granuloma in occipital lobe
Colover [7]						
Case 3	23	F	.....	Dulness, lethargy, headache, vomiting, papilledema, 2 yr.	Increased protein; pleocytosis	* Granulomata, with adhesions, in posterior fossa; hydrocephalus (ventriculogram)
Aszkanazy [2f]						
Case 2	30	F	.....	Diabetes insipidus, bitemporal hemianopsia, weak legs, 5 yr.	Increased protein	Granulomata involving optic nerves and chiasm, infiltrating floor of 3d ventricle
Case 4	23	M	.....	Focal seizures, 14 yr.	.....	* Granulomata of leptomeninges, falx; cortical scars right central area
Case 5	41	F	.....	Primary optic atrophy, bitemporal hemianopsia, 2 yr.	.....	* Granulomata of optic nerves and chiasm; infiltration of floor of 3d ventricle

* Operation.

does not invade cerebral parenchyma but surrounds and compresses cranial nerves and the optic chiasm, giving rise to obstructive hydrocephalus, papilledema, and optic nerve atrophy. In more acute forms the meningeal vessels may be severely affected, resulting in thrombosis, infarction, cerebral edema, and fulminating signs of increased intracranial pressure. The second variety is more circumscribed, with large granulomata in the brain parenchyma, as well as leptomeningeal involvement and granular ependymitis. The dura is rarely involved, probably not without leptomeningeal or parenchymal extension.

In the accompanying Table we have summarized the reported cases of sarcoidosis of the central nervous system in which the diagnosis has been clearly established by biopsy or autopsy.[5] We wish to emphasize the frequency with which sarcoid granulomata of the central nervous system are reported to be perivascular.

A few other cases with autopsy which are mentioned in the literature have not been included in the tabular summary because the data are less complete. Bang [6] found multiple "tuberculoma" in the cerebrum, cerebellum, and pons in a case of uveoparotid fever complicated by convulsions in which autopsy was done. In the discussion on Zollinger and von Meyenburg's [5f] case, Scheidigger, Uehlinger, and Nicod each mentioned a case of cerebral localization of sarcoid. Patry [7] described a case of sarcoid affecting the meninges, ependyma, and choroid plexus. Ricker and Clark [8] mentioned three cases in which necropsy showed healed and healing sarcoid lesions in the brain and meninges; in one case there were arteritic and periarteritic lesions of small and medium-sized arteries. Longcope and Freiman [4b] described two cases of fulminating and rapidly fatal cerebral sarcoidosis. The dura was involved in one and the pituitary and the hypothalamic region in the other.

The clinical symptoms in the reported cases corresponded closely to the pathological changes. Headache, nausea, vomiting, optic nerve atrophy, bitemporal hemianopsia, cranial nerve paralyses, papilledema, and meningeal irritation pointed to a diffuse obstructive and infiltrative process in the leptomeninges. Seizures, hemiplegias, pareses, and homonymous hemianopsia pointed to a focal pathological

5. (*a*) Strasmann: Über seltene, sehr chronische Verlaufsform tuberkulöser Meningitis, Mitt. Grenzgeb. Med. u. Chir. **23**:351-366, 1911. (*b*) Simons, A., and Merkel, H.: Zur Kenntnis der chronischen tuberkulösen Zerebrospinalmeningitis, Neurol. Centralbl. **36**:258-277, 1917. (*c*) Lenartowicz, J., and Rothfeld, J.: Ein Fall von Hautsarkoiden (Darier-Roussy) mit identischen Veränderungen im Gehirn und den inneren Organen, Arch. Dermat. u. Syph. **161**:504-519, 1930. (*d*) Naumann, O.: Kasuistischer Beitrag zur Kenntnis der Schaumannschen "benignen granulomatose" (Morbus Besnier-Boeck-Schaumann), Ztschr. Kinderh. **66**:1-8, 1938. (*e*) Erickson, Odom, and Stern.[3a] (*f*) Zollinger, H., and von Meyenburg: Über eigenartige perivaskuläre Granulomatose des Gehirns, Schweiz. med. Wchnschr. **72**:825-826, 1942. (*g*) Zollinger, H.: Demonstration: 2 Fälle von grosszellig-sklerosierender Lymphangitis cerebri (Morbus Boeck), ibid. **72**:1136, 1942. (*h*) Zahn, P., and Weber, G.: Beitrag zur Kenntnis der chronischen Meningoenzephalitis unter besonderer Berücksichtigung der Besnier-Boeckschen Granulomatose, Confinia neurol. **8**:9-38, 1947-1948. (*i*) Everts, W. H.: Sarcoidosis with Brain Tumor, Tr. Am. Neurol. A. **72**:128-130, 1947. (*j*) Colover.[1] (*k*) Aszkanazy.[3f]

6. Bang, S.: Febris uveo-parotidea, Ugesk. læger **80**:571-578, 1918.

7. Patry: Dissertation, Lausanne, 1943; cited by Leitner, S. J.: Der Morbus Besnier-Boeck-Schaumann: Chronische epitheloidzellige Reticuloendotheliose oder Granulomatose, Ed. 2, Basle, Switzerland, Benno Schwabe & Co., 1949.

8. Ricker, W., and Clark, M.: Sarcoidosis: A Clinico-Pathologic Review of 300 Cases, Including 22 Autopsies, Am. J. Clin. Path. **19**:725-749, 1949.

process in the brain parenchyma. Both the diffuse leptomeningeal and the circumscribed parenchymal type might run courses of weeks' to years' duration. Generally, however, unlike the present case, the process was chronic.

Such symptom complexes are, of course, nonspecific and represent the kind of diagnostic problem which frequently confronts the neurologist. A review of the literature and a consideration of the present case, however, point to the wisdom of routine investigations for sarcoidosis when one is confronted with clinical problems of the two types described. Such a case should be reviewed for past or present lesions of the skin, for evidence of pulmonary or bony sarcoidosis, and for alterations in blood globulins, a negative reaction to tuberculin, and an increased sedimentation rate. Biopsy of involved tissue may be diagnostic. In involvement of the central nervous system by sarcoidosis the cerebrospinal fluid is frequently under increased pressure, with elevated total protein and globulin levels, moderate pleocytosis, and, rarely, xanthochromia. The chloride content is unaltered; the sugar may be decreased.

Two other clinical syndromes may be produced by sarcoidosis of the central nervous system and often present a great diagnostic problem to the neurologist: (*1*) "pseudotumor," a recently discussed syndrome of various origins,[9] simulating brain tumor, and (*2*) "chronic chiasmatic arachnoiditis." Not infrequently compression of the optic chiasm by tumor may be suspected, but operation reveals a thickened arachnoid around the optic chiasm. In such cases sarcoidosis should be excluded.

The striking distribution of the granulomata in the meninges in our case prompted us to seek similar mention of this in the cases of cerebral involvement described in the literature. In virtually all instances in which careful histological study had been made the frequent perivascular distribution of the granulomata and proliferation of the reticulum had been noted, as was evident in our case.

The lesions reported here and those described as allergic granulomatosis[10] show similarities, as well as essential differences. The similarities are of particular interest, because it has been postulated by some investigators that in certain cases of sarcoidosis an underlying hyperergic tissue response to some unidentified etiologic agent, including the tubercle bacillus, may be the cause.[11] Evidence in support of this concept is the demonstration of acute arteritic lesions in sarcoidosis.[12]

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9. Denny-Brown, D. E.: The Changing Pattern of Neurologic Medicine, New England J. Med. **246**:839-846, 1952.

10. (*a*) Newman, W., and Wolf, A.: Non-Infectious Granulomatous Angiitis Involving the Central Nervous System, read before the American Association of Neuropathologists, Atlantic City, N. J., May 7, 1952. (*b*) Zuelzer, W. W., and Apt, L.: Disseminated Visceral Lesions Associated with Extreme Eosinophilia: Pathological and Clinical Observations on Syndrome of Young Children, Am. J. Dis. Child. **78**:153-181, 1949. (*c*) Perlingiero, J. G., and György, P.: Chronic Eosinophilia: Report of a Case with Necrosis of the Liver, Pulmonary Infiltrations, Anemia and Ascaris Infestation, ibid. **73**:34-43, 1947. (*d*) Churg, J., and Strauss, L.: Allergic Granulomatosis, abstracted, Am. J. Path. **25**:817, 1949; (*e*) Allergic Granulomatosis, Allergic Angiitis, and Periarteritis Nodosa, ibid. **27**:277-301, 1951.

11. (*a*) Teilum, G.: Allergic Hyperglobulinosis and Hyalinosis (Paramyloidosis) in the Reticulo-Endothelial System in Boeck's Sarcoid and Other Conditions, Am. J. Path. **24**:389-407, 1948. (*b*) Lewis, G. E.; Raines, R., and Stewart, D. S.: Uveoparotitis, Lancet **2**:1204-1206, 1936.

12. Jacques,[2b] Loncope and others.[4]

Why the lesions should be confined to the adventitia and to perivascular regions is not clear, but these tissues, together with the meninges, are the only ones in the central nervous system which are rich in collagen. Recently, it has been shown that after injection antigenic substances of a widely different type may be demonstrated in the walls of blood vessels, including those of the central nervous system.[13] The morphological nature of the involvement of the central nervous system in sarcoidosis does not disprove the hypothesis that sarcoid represents a disorder of tissue antigen-antibody response.

SUMMARY

A case, with necropsy observations, of an unusually acute form of sarcoidosis of the central nervous system is reported.

The patient was admitted with sudden onset of rapidly increasing intracranial pressure, simulating an intracranial space-occupying lesion.

Spiculated giant-cell granulomata in the lungs, lymph nodes, kidneys, and liver and granulomatous giant-cell angiitis and perjangiitis of the meninges were present.

The natural history and pathology of intracranial sarcoidosis are discussed.

13. (*a*) Kaplan, M. H.; Coons, A. H., and Deane, H. W.: Localization of Antigen in Tissue Cells: Cellular Distribution of Pneumococcal Polysaccharides Types II and III in the Mouse, J. Exper. Med. **91**:15-30, 1950. (*b*) Coons, A. H.; Leduc, E. H., and Kaplan, M. H.: Localization of Antigen in Tissue Cells, Fate of Injected Foreign Proteins in the Mouse, ibid. **93**:173-188, 1951.

CARDIOVASCULAR CHANGES ASSOCIATED WITH ELECTRO-CONVULSIVE THERAPY IN MAN

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THE DEVELOPMENT of an electromagnetic blood-flow meter by Richardson and associates [1] enabled the accurate direct, continuous recording of blood flow in the carotid artery of animals. This method was employed in a recent study by Brown and others [2] in which dogs were subjected to electroconvulsive shock and, more recently, in a study of the cardiovascular response of monkeys undergoing electroconvulsive shock.[3] In both studies the blood pressure also was measured directly in the arteries of the animals. In the two series of experiments on dogs and monkeys, it was found that the pattern of blood flow response following the onset of electroconvulsive shock duplicated the pattern of blood pressure response, as to both time and direction of change. It was suggested in the study on monkeys that this finding had important implications for the interpretation of certain responses observed in human subjects receiving electroconvulsive therapy. At present this method of measuring blood flow is not easily applicable to human subjects because it requires surgical cannulation of the carotid artery. On the basis of the uniform results from the two studies on animals, it was concluded that in man the cerebral blood flow response should follow the same pattern as the arterial pressure response to electroconvulsive therapy. This interpretation would appear

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Read in modified form at the autumn meeting of the American Physiological Society, New Orleans, Sept. 5, 1952.

Recording equipment used in this study was made available by the Aero Medical Laboratory, Wright Air Development Center, Air Research and Development Command.

James Kennedy, M.D.; Margaret Emmons, M.D.; Jean Butler, R.N., and Jeanne Schumacher, R.N., gave valuable assistance during the performance of this experiment. Lucien Morris, M.D., and M. L. Frederickson, M.D., of the Department of Anesthesia, carried out complete curarization on four patients.

1. Richardson, A. W., and others: A Newly Developed Electromagnetic Flow Meter, J. Lab. & Clin. Med. **34**:1706, 1949.

2. Brown, M. L., and others: Changes in Blood Flow, Blood Pressure and Cardiac Rate Associated with Electroconvulsive Shock, Am. J. Psychiat. **109**:27, 1952.

3. Brown, M., and others: Cardiovascular Changes Associated with Electroconvulsive Shock in Monkeys: Cerebral Blood Flow, Blood Pressure, and Cardiac Rate Measurements Before, During, and After Electroconvulsive Shock, A. M. A. Arch. Neurol. & Psychiat., this issue, p. 609.

to apply particularly if in man the blood pressure response to electroconvulsive therapy exhibited a pattern of change similar in time and direction to that observed in the animals subjected to electroconvulsive shock.

In the present investigation the arterial blood pressure responses were measured in a series of psychotic patients undergoing electroconvulsive therapy to determine whether or not the blood pressure pattern was similar to that observed in the two previous studies on dogs and monkeys.

MATERIAL AND METHODS

Twenty-four hospitalized psychotic patients were studied in a series of 31 electroconvulsive shock treatments; the group included 9 men and 15 women, with an age range of 22 to 75 years; the disease in 9 patients had been diagnosed as schizophrenia, and that in 15, as depression. Arterial blood pressure was directly and continuously recorded before, during, and after the application of the electrical stimulus. Direct blood pressure measurements were obtained in the following manner: A No. 18 thin-walled hypodermic needle was used to make a puncture in either the brachial or the femoral artery. A nylon catheter was then passed through the bore of the needle into the lumen of the artery; the needle was removed from the artery by sliding it back over the catheter. The other end of the catheter was attached to a Statham arterial-pressure gage, which recorded blood pressure changes on an Offner dynograph recorder.

After cannulation, the patient continued to lie quietly on the treatment table until a steady state of blood pressure had been maintained for 5 to 10 minutes. At the end of this period each patient received curare (tubocurarine chloride U.S.P.) intravenously; the dosage was calculated at 0.5 cc. per 40 lb. (18 kg.) of body weight. This standard procedure was used to avoid fractures during the convulsions. Within two to five minutes after the administration of curare the treatment was given, a standard Offner No. 733 electrotherapy apparatus being used.

The milliamperes and volts delivered to the patient were recorded on the dynograph. The durations of the convulsions and the respiratory arrest were timed with stop watches. At the cessation of the convulsions, oxygen was administered for 30 to 120 seconds to minimize cyanosis. Blood pressure recording was continued for 20 to 30 minutes after the convulsion.

Each patient was used as his own control with reference to the measurements of arterial blood pressure and cardiac rate. The means of the systolic and diastolic pressures and the cardiac rate obtained during the interval after curare and before electroconvulsive therapy were used as control values. The deviations from these values following electroconvulsive therapy are the results reported in this study. The cardiac rate was obtained from the blood pressure recordings.

A major convulsion and respiratory arrest were produced in each of the 31 treatments, although 15 patients required two or more shocks before a major reaction was induced. As a consequence, readings were obtained on 28 subconvulsive reactions.

Four of the patients (two with schizophrenia and two with depression) were also studied while completely curarized (dose 10 cc.) to evaluate the effect of convulsive movements upon the blood pressure. These four patients were maintained on artificial respiration by bag and mask with 100% O_2 delivered at the rate of about 10 liters per minute while respiratory paralysis was present, and until adequate respiratory movements were resumed by the patient, 20 to 40 minutes after shock. Although the gross convulsive movements were abolished by the curare, the duration of the tonic and of the clonic phases was observed from twitching movements of the toes.

The means of the recorded milliamperes, volts, and duration of shock stimulus, in seconds, delivered to all three groups of patients were 374, 83, and 0.47 respectively. For the 31 major reactions the mean duration of the convulsions was 45 seconds; for the four complete curarizations it was 61 seconds. The mean respiratory arrest for the 31 major reactions was 52 seconds.

RESULTS

For about a week before the experimental day, blood pressure readings by sphygmomanometer were obtained on each patient, before arising and after retiring. It was found that blood pressure readings obtained by the use of a cuff were within

a few millimeters of mercury of the values obtained by direct recording. Thus, the mean daily cuff reading provided a basis for estimating how much the preshock control blood pressure was increased as a result of apprehension in the patient concerning the experimental procedure.

The average control blood pressures and pulse rates for the 31 treatments were as follows: ward readings: blood pressure 129/76, pulse rate 76; precurare readings: blood pressure 155/88, pulse rate 94; preshock readings: blood pressure 159/92, pulse rate 105. The experimental situation appears to have added, presumably through apprehension, an increase in blood pressure and pulse rate over the resting state in the ward.

The values given below are significant at the 0.1 to 5% level of confidence unless otherwise indicated.

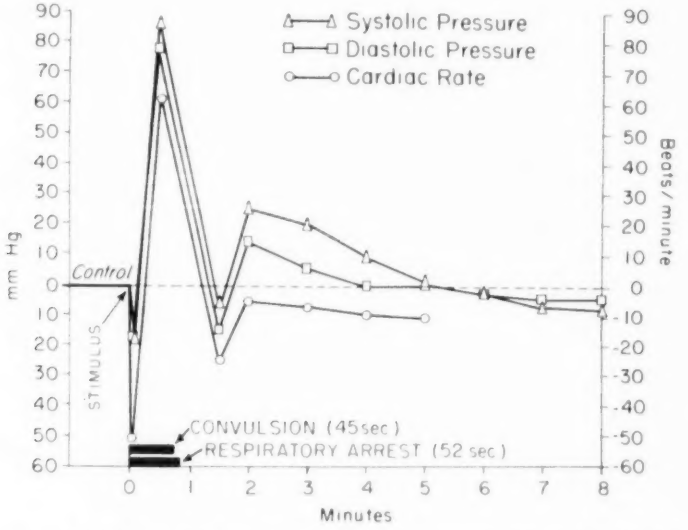

Chart 1.—Mean changes in direct blood pressure and cardiac rate in a series of 31 major reactions following electroconvulsive therapy.

The 31 experiments on patients exhibiting major reactions to electroshock therapy resulted in the following pattern of change in arterial blood pressure after the onset of the stimulus (Chart 1): During the first three seconds after shock, the mean systolic pressure decreased 18 mm. below the control level, and the mean diastolic pressure decreased 16 mm. below the control level. This was followed by elevation to a peak of 85 mm. above the control level for systolic pressure and 78 mm. above the control level for diastolic pressure 30 seconds after shock. While the mean convulsion and respiratory arrest continued, the mean systolic and diastolic pressures began to decline; when the convulsions had ceased and respiration was resumed, the systolic and diastolic pressures continued to decline and reached a secondary drop of 7 and 15 mm. respectively below the control level one and one-half minutes after shock. Though this secondary drop in systolic pressure was only significant at the 30% level of confidence, 25 of the 31 records showed the second

decrease in pressure. The decrease in arterial pressure was followed by a second increase above the control pressure, reaching a peak of 24 mm. for systolic pressure and 14 mm. for diastolic pressure at two minutes after shock. Mean arterial pressures then began a gradual decline and six minutes after shock were a few millimeters below control level, where they remained until the end of the recording period, 20 to 30 minutes after shock.

Within the first three seconds after shock (Chart 1), the mean cardiac rate decreased to 51 beats a minute below the control rate; this was followed by an increase to a peak of 61 a minute above the control rate 30 seconds after shock. Thereafter, the cardiac rate rapidly declined to values below the control rate and fluctuated below control level until the end of the recording period. After the cessation of the convulsions, cardiac arrhythmia was present in the majority of records and sometimes lasted throughout the recording period.

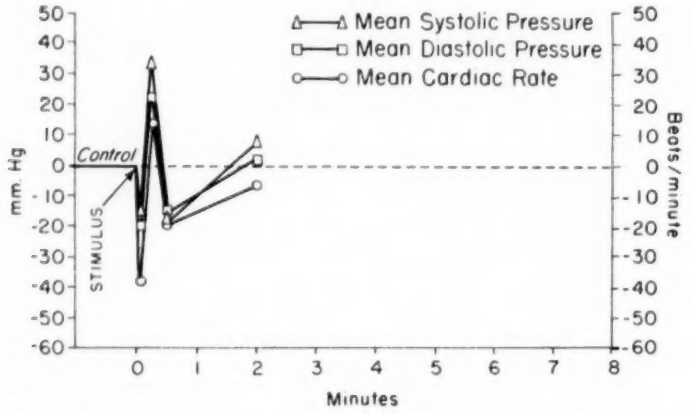

Chart 2.—Mean changes in direct blood pressure and cardiac rate in a series of 28 subconvulsive reactions following electroconvulsive therapy.

Fifteen patients experienced 28 subconvulsive shocks. The arterial pressure pattern of these 28 subconvulsive reactions (Chart 2) resembled that of the 31 major reactions, the only difference being the magnitude of the response. The mean systolic and diastolic pressures dropped 16 and 19 mm. respectively below control levels during the first three seconds after shock. This was followed by an increase above the control level to peak values of 33 mm. for systolic and 23 mm. for diastolic pressure within 20 seconds after shock. Within 40 seconds after shock both systolic and diastolic pressures exhibited a secondary decrease of 18 and 16 mm. respectively below control pressures. The arterial pressures then increased to secondary peaks above control pressures of 7 mm. for the systolic and 2 mm. for the diastolic pressure two minutes after shock. Most of the records returned to control levels of arterial pressure within a few minutes after shock.

In the 28 subconvulsive reactions to electroconvulsive therapy, the cardiac rate response pattern resembled the blood pressure pattern (Chart 2). During the first 3 seconds after shock the mean cardiac rate decreased 39 beats a minute below the control rate; at 20 seconds it rose to 14 a minute above the control rate; at 40

seconds it dropped to 19 a minute below the control rate, and at two minutes the rate was 7 a minute below the control rate. The cardiac rate for the 28 records tended to return to the control rate within a few minutes after shock. The accompanying Table gives the absolute mean values for the blood pressure and the heart rate at various intervals during the experiment for the series of 31 major reactions and for the series of 28 subconvulsive reactions.

The arterial pressure responses to electroconvulsive therapy of the four fully curarized patients exhibited a pattern which was similar to that of the 31 major reactions. In the statistical analysis of the four records, only one change in blood pressure following electroconvulsive therapy proved significant at less than the 1% level, i. e., the initial marked increase in systolic and diastolic pressures to absolute peaks of 252 and 158 mm. Hg respectively, or 83 and 53 mm. Hg respectively above the control level, 30 seconds after shock. In these records, all other changes in blood pressure following electroconvulsive therapy showed a statistical significance at approximately the 20% level of confidence. The initial decrease in mean systolic pressure following the beginning of electroconvulsive therapy was exhibited in two of the four records; three of the four records showed the initial decline in

Absolute Mean Values for Blood Pressure and Cardiac Rate at Various Intervals Before and After Electroconvulsive Therapy

Means for 31 Major Reactions				Means for 28 Subconvulsive Reactions			
Time	Systolic Pressure, Mm. Hg	Diastolic Pressure, Mm. Hg	Heart Rate, Beats/ Min.	Time	Systolic Pressure, Mm. Hg	Diastolic Pressure, Mm. Hg	Heart Rate, Beats/ Min.
After curare (control)	159	92	105	After curare (control)	159	92	105
3 sec. after ECT	141	76	54	3 sec. after ECT	143	78	66
30 sec. after ECT	244	170	166	20 sec. after ECT	192	115	119
90 sec. after ECT	152	77	78	40 sec. after ECT	141	76	86
120 sec. after ECT	183	106	98	120 sec. after ECT	166	94	98

mean diastolic pressure. All four records displayed the subsequent pronounced elevation in arterial pressures. The second decrease in pressures was present in all four records; the secondary increase in pressures was present in three of the four systolic responses and in two of the four diastolic responses. The mean arterial pressures gradually declined below control levels in 4 minutes, remaining below control pressures until about 12 minutes after shock; then they gradually increased to a moderate height above the control level and remained several millimeters of mercury above this level until the end of the recording period, about 30 minutes after shock.

In the initial stages of the response to electroconvulsive therapy the cardiac rate of the four fully curarized patients followed a pattern similar to that of the blood pressure. The marked elevation of rate above the control value was significant at less than the 1% level of confidence. The initial decrease and the secondary decrease were significant at more than the 5% level. The cardiac rate remained below the control level throughout the 30-minute postshock recording period.

The cardiovascular pattern obtained from one fully curarized patient who had a subconvulsive reaction to electroconvulsive therapy resembled the pattern described for the 28 subconvulsive reactions.

COMMENT

The evidence from this investigation on human subjects is similar to that obtained in the previous studies on dogs and monkeys subjected to electroconvulsive shock. Since it has been demonstrated in both dogs and monkeys that the cerebral blood flow pattern duplicates the blood pressure pattern in response to electroconvulsive shock, it seems reasonable to assume that in man a similar relation exists between blood flow and blood pressure after electroconvulsive therapy. If this hypothesis is correct, one would expect a great elevation in cerebral blood flow during the clonic phase of the convulsion, followed by a decrease in flow at the end of the convulsion and a second increase in cerebral flow during the period in which respiration is resumed and relaxation begun. The cerebral blood flow would then be assumed to decline gradually below the control level, returning to that level, or remaining slightly above or below, at about 20 to 30 minutes after shock. A momentary peripheral vasodilatation may be responsible for the secondary decrease in the blood pressure pattern, with peripheral vasoconstriction resuming dominance in the secondary peak. The evidence against extensive cerebral vasoconstriction has been presented by Brown and associates.[3]

Kennedy and co-workers[4] reported observations on the exposed parietal cortex of an anesthetized patient during an epileptic seizure. The pattern of color changes observed, i.e., blanching and reddening of the cortex, agrees with the pattern of blood pressure response to electroconvulsive therapy reported in this paper. This finding supports the hypothesis suggested above regarding changes in cerebral blood flow in man following electroconvulsive therapy.

Woodbury and associates[5] found that after a convulsant dose of pentylene tetrazol U.S.P. (metrazol®) in dogs and man the arterial pressure increased during the tonic phase and reached a peak elevation during the clonic phase of the convulsion. The importance of the convulsions in their effect on arterial pressure changes, as well as the depressant effects of paralyzing doses of curare on blood pressure, which they reported have not been confirmed by us.

The cardiovascular response pattern to electroconvulsive therapy has been found to be similar for major reactions, subconvulsive reactions, and reactions during complete curarization. Thus, it appears that this general response pattern is due to the effects of the electrical stimulus alone, and not to any gross motor activity which may occur as the result of such stimulation. Apparently, the convulsions have no augmenting influence on the circulatory response, since there was no difference between the magnitude of the blood pressure response in the four fully curarized patients and that in the series of 31 major convulsions. In individual cases, it was found that a greater shock stimulus was required to produce a greater magnitude of cardiovascular response. On this basis, one could explain the observed difference between the subconvulsive and the convulsive group with respect to magnitude of pressure response, a slight stimulation of the patient producing a subdued magnitude of pressure response and a greater stimulation producing an increased magnitude.

4. Kennedy, F., and others: Clinical Evidence for Cerebral Vasomotor Changes, A. Res. Nerv. & Ment. Dis. Proc. **18**:670, 1938.

5. Woodbury, R. A., and others: Effect of Metrazol upon the Blood Pressure of Man and Dogs, J. Pharmacol. & Exper. Therap. **73**:431, 1941.

Gordh and Silfverskiöld[6] suggested that changes in intrathoracic and intra-abdominal pressures in man produce the circulatory disturbances observed to follow electroconvulsive therapy. The data on the four fully curarized patients do not substantiate this hypothesis. The same marked changes in blood pressure and cardiac rate occurred in these four patients as were observed in the 31 treatments involving major reactions to electroconvulsive therapy. Since the fully curarized patients were completely relaxed during the entire period of response to electroconvulsive therapy, marked changes in pressure in the body cavities could not account for the observed changes in circulation.

Krämer[7] stated that diastolic pressure was less influenced than systolic pressure in electroconvulsive therapy, and that blood pressure changes were less pronounced in patients with higher pretreatment pressures. Neither result was confirmed in the present study. In 31 electroconvulsive shock treatments producing major reactions, the mean percentage changes in diastolic pressure were greater than the mean percentage changes in systolic pressure except during the postconvulsive period of relaxation. The mean percentage changes in systolic and diastolic pressures respectively during the three time intervals of the convulsion were as follows: 12 and 18%, below control level; 55 and 87%, above control level, and 1 and 14%, below control level. No correlation was found between the pretreatment level of blood pressure and the extent of the blood pressure rise during electroconvulsive therapy. For example, four patients exhibited the following changes in blood pressure respectively: control pressure 180/86; peak elevation during the convulsion 318/130; difference 138/44; control pressure 127/90, peak 180/150, difference 53/60; control pressure 130/83, peak 273/193, difference 143/110; control pressure 192/96, peak 300/210, difference 108/114. It is doubtful whether the extent of blood pressure increase in electroconvulsive therapy is limited by high pretreatment levels.

In our study, the mean precurare pressures are lower than the mean preshock blood pressures. However, the individual blood pressure responses to curare were not consistent: Some patients showed no change in blood pressure after curare; others showed a fall, and still others exhibited an increase. On the basis of such variable results, it is suggested that perhaps curare itself has no direct influence on blood pressure, but, rather, that the changes in pressure could be due to apprehension related to curarization and the electroconvulsive therapy.

In a monograph on the effects of curare, McIntyre[8] concluded that curarization with tubocurarine "can occur with little or no manifestation of hemodynamic disturbance." Apprehension is probably involved also in the differences observed between ward pressures and those recorded before curare was given in the experimental situation.

The cardiac response to electroconvulsive therapy was an initial bradycardia in the early tonic phase, tachycardia in the clonic phase, and arrhythmia, of several minutes' duration, in the postconvulsive period. These results agree with

6. Gordh, T., and Silfverskiöld, B. P.: Disturbance of Circulation in Convulsions of Epileptic Type: I. Intrathoracic and Intra-Abdominal Pressure During Electroshock, Acta med. scandinav. **113**:183, 1943.

7. Krämer, R.: Electroshock and Blood Pressure, Nervenarzt **21**:221, 1950.

8. McIntyre, A. R.: Curare: Its History, Nature, and Clinical Use, Chicago, University of Chicago Press, 1947, p. 125.

the findings of other investigators, such as Altschule and associates.[9] In the work of Brown and associates,[2] the bradycardia and arrhythmia were shown to be of vagal origin.

SUMMARY AND CONCLUSIONS

The arterial blood pressure response to electroconvulsive therapy in man followed a pattern similar to that observed in dogs and monkeys subjected to electroconvulsive shock. Since it was found that the cerebral blood flow pattern duplicated the blood pressure pattern following electroconvulsive shock in animals, it is assumed that unless a different relation between blood flow and blood pressure can be demonstrated in man than exists in these animals, the cerebral blood flow response in man should follow the same pattern as the blood pressure response to electroconvulsive therapy.

The blood pressure response to electroconvulsive therapy in man exhibited an initial decrease below control levels during the early tonic phase, followed by a marked elevation above the control level during the late tonic and throughout the clonic phase of the convulsion. The blood pressure began to decline while the convulsion and the respiratory arrest continued; a secondary decrease below control pressure was reached shortly after the end of the convulsion, and this was followed by a secondary increase to a peak above the control level within two minutes after shock. The arterial pressure then decreased gradually, returning to the control level, or remaining only slightly above or below that level within 20 to 30 minutes after shock. This general pattern of response was found in 31 treatments evoking a major reaction to electroconvulsive therapy, in 4 treatments administered to fully curarized patients who gave evidence of a major reaction to electroconvulsive therapy, in 28 subconvulsive treatments, and in a subconvulsive shock treatment given 1 fully curarized patient.

The similarity in the blood pressure response patterns in the three groups of patients, namely, patients showing major reactions, patients having subconvulsive reactions, and fully curarized patients, indicates that the cardiovascular changes following electroconvulsive therapy are independent of the convulsions and appear to result from the effects of the electroshock stimulus alone.

The marked and prolonged elevation in arterial pressure following the onset of the shock stimulus indicates a marked increase in cerebral blood flow during this time, thus making it improbable that extensive cerebral vasoconstriction occurs.

No correlation was found between the pretreatment level of blood pressure and the height of blood pressure elevation during electroconvulsive therapy.

During the convulsion, diastolic pressure exhibited a greater percentage increase than did systolic pressure.

It appears that curare (tubocurarine) per se does not produce marked changes in blood pressure in man.

9. Altschule, M. D., and others: Significance of Changes in the Electrocardiogram After Electrically Induced Convulsions in Man, Arch. Neurol. & Psychiat. **58**:716, 1947.

CARDIOVASCULAR CHANGES ASSOCIATED WITH ELECTROCONVULSIVE SHOCK IN MONKEYS

Cerebral Blood Flow, Blood Pressure, and Cardiac Rate Measurements Before, During, and After Electroconvulsive Shock

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IN A RECENT paper [1] we reported the results of a series of experiments on dogs in which we measured directly the changes in carotid blood flow, arterial pressure, and cardiac rate associated with electroconvulsive shock. This method of measuring blood flow, in which we used an electromagnetic blood-flow meter,[2] is not applicable to the human subject, since it requires the cannulation of the carotid artery. In the anatomy of the dog, there is a vascular network, the rete mirabile, that provides connections between the intracranial and the extracranial blood vessels.[3] Since this vascular system is not present in man, it was desirable that the results obtained on dogs be verified by similar experiments performed on animals having a closer anatomical relationship to man. For this purpose, the rhesus macaque was the animal of choice in the present study. It was reasoned that if a pattern of cardiovascular response to electroconvulsive shock was exhibited in monkeys similar to that found in dogs, one might, with greater confidence extend to man the conclusions based on these results.

MATERIAL AND METHODS

Several weeks prior to the experiments, the external carotid artery was ligated in 10 rhesus monkeys and the operative sites were allowed to heal. This procedure permitted the recording of internal carotid blood flow in the common carotid artery. Since the internal carotid artery delivers blood only to cerebral vessels, this measurement was interpreted as an index of cerebral

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Read in modified form at the autumn meeting of the American Physiological Society, New Orleans, Sept. 5, 1952.

The recording equipment used in this study was made available by the Aero Medical Laboratory, Wright Air Development Center, Air Research and Development Command.

1. Brown, M. L., and others: Changes in Blood Flow, Blood Pressure and Cardiac Rate Associated with Electroconvulsive Shock, Am. J. Psychiat. **109**:27, 1952.

2. Richardson, A. W., and others: A Newly Developed Electromagnetic Flow Meter, J. Lab. & Clin. Med. **34**:1706, 1949.

3. Batson, O. V.: Anatomical Problems Concerned in the Study of Cerebral Blood Flow, Fed. Proc. **3**:139, 1944.

blood flow. The blood flow was measured in the internal carotid artery of 10 rhesus monkeys by means of an electromagnetic blood-flow meter.[2] The blood flow was recorded on an Offner dynograph recorder. Direct arterial pressure was recorded from the same site in the vascular bed as was blood flow, by means of a Statham arterial-pressure gage—Offner recorder system attached to a T in a lucite® blood-flow pick-up. The cardiac rate was obtained from the pressure records. All surgical operations were performed while the animal was under chloralose anesthesia (75 to 100 mg. per kilogram of body weight). Propylene glycol was used as a solvent for α-chloralose, and the anesthetic was administered intraperitoneally. Alpha-chloralose was selected as a suitable anesthetic in that it produced surgical anesthesia without suppression of the convulsive response. A standard dose of 3 cc. of heparin was injected intravenously into each animal to prevent blood clotting in the cannulas.

The Offner No. 710 electrotherapy apparatus was used to deliver the shock stimulus. The current was delivered to the bitemporal region of the head by means of two small electrodes attached to a forceps-like clamp held by the operator. The voltage, current, and duration of the stimulus were recorded directly on two channels of the Offner Dynograph adapted to function as a recording voltmeter and milliameter. The duration of the stimulus could be calculated from the 60-cps wave pattern recorded.

Five female and five male monkeys were used in the study. The weights ranged from 4.4 to 5.8 kg., with a mean weight of 4.9 kg. The ranges and means for components of the shock stimulus recorded for the 10 animals were 104 to 299 ma., with a mean of 210 ma., and 61 to 130 volts, with a mean of 80 volts. Duration of the shock was held constant at 0.5 second.

A major convulsion and respiratory arrest occurred in each animal immediately after the onset of the shock stimulus. The duration of the convulsions ranged from 24 to 50 seconds, with a mean of 38 seconds; the length of the respiratory arrest ranged from 27 to 60 seconds, with a mean of 41 seconds. All 10 animals appeared to be in a sleep-like state after the convulsion ceased and did not awaken before the experiment ended, some 30 minutes after shock.

Recording of the blood flow and pressure was continuous prior to, during, and after the appliion of the electroshock stimulus. Each animal was used as its own control with reference to measurements of blood flow, arterial pressure, and cardiac rate. All changes in these three measurements are reported as percentage variations from control values obtained during a 15-minute steady state preceding the application of the shock stimulus.

RESULTS

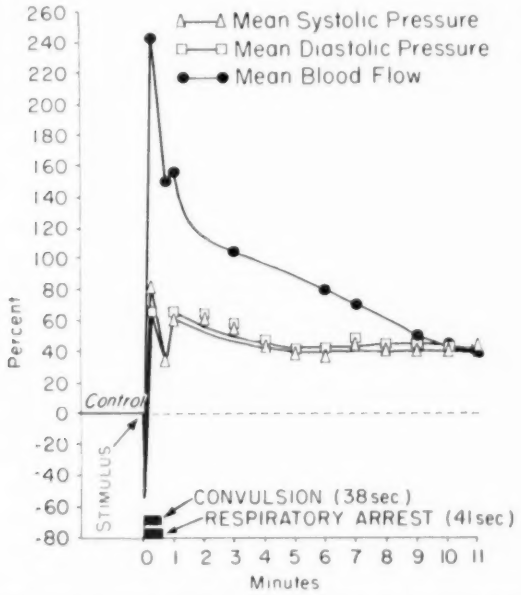
In a statistical analysis of the data, all values were found significant between the 0.1% and the 5% level of confidence.

For the series of 10 monkeys, the mean control blood flow in one of the internal carotid arteries was 15 cc. a minute, with a range of 7 to 24 cc. a minute. The mean control systolic pressure was 88 mm. Hg, with a range of 73 to 120 mm. Hg. The mean control diastolic pressure was 64 mm. Hg, with a range of 58 to 80 mm. Hg. The mean control cardiac rate was 161 beats a minute, with a range of 144 to 186 beats a minute.

The significant changes in mean internal carotid blood flow after the onset of electroconvulsive shock were as follows: During the first 3 seconds after shock, there was an immediate decrement in mean blood flow of 57% below the control level; this was followed by an increase in mean flow to a peak of 244% above control level at 30 seconds after shock. While the convulsion and respiratory arrest continued, the mean blood flow in the internal carotid artery decreased; the flow continued to decline after the convulsion had ceased, and a secondary depth of 149% above control level was reached 45 seconds after shock. Respiration was resumed during this period. This secondary decline was followed by a second-

ary increase in mean blood flow to a peak of 156% above control level one minute after shock. The mean blood flow then resumed a gradual descent. The blood flow of the 10 monkeys had returned to control levels 30 minutes after shock.

The changes in mean arterial pressure following electroconvulsive shock exhibited a pattern similar to that described for the mean blood flow. The initial response to electroconvulsive shock consisted in an abrupt fall in mean systolic and diastolic pressures to 11 and 31% respectively below control pressures. At 30 seconds after shock the mean systolic pressure had increased to a peak elevation of 81% above control level, and the mean diastolic pressure had increased to a peak of 66% above the control. While the convulsion and respiratory arrest con-



Percentage changes in mean blood flow and mean blood pressure following electroconvulsive shock in 10 rhesus monkeys.

tinued, the mean systolic and diastolic pressures began to decline. At the end of the convulsion the decline continued and reached a secondary depth of 37 and 33% respectively above control pressures 45 seconds after shock. Respiration was resumed during this time. The fall in arterial pressures was followed by a secondary increase above the control level to peaks of 62% for systolic pressure and 65% for diastolic pressure one minute after shock. Mean arterial pressures then began to decline gradually, and 30 minutes after shock the arterial pressures of the 10 animals either had reached or were a few per cent above control levels. The Chart is a graphic representation of the changes in blood flow and blood pressure following electroconvulsive shock.

The mean cardiac rate decreased to 63% below control levels in the first three seconds after shock; this was followed by an increase in rate to a peak value of

33% above control levels 30 seconds after shock. Thereafter, the mean cardiac rate began an irregular decline toward control levels. At 30 minutes after shock the cardiac rate of the 10 animals either had returned to or were a few per cent above control levels.

One animal had a respiratory arrest which lasted 3 minutes 40 seconds. The animal was revived by artificial respiration. The cause of the respiratory arrest was undetermined.

COMMENT

The cardiovascular response pattern to electroconvulsive shock in monkeys follows a pattern similar to that exhibited by dogs subjected to electroconvulsive shock,[1] with one exception: The blood flow and blood pressure pattern in monkeys showed a secondary decrease at the end of the seizure, followed by a secondary increase. This secondary increase was not observed in the response pattern of dogs at the cessation of the convulsions. The mean durations of the convulsion and respiratory arrest were shorter in the dogs—33 and 25 seconds respectively—than in the monkeys, 38 and 41 seconds respectively. An explanation of this observed difference in cardiovascular response pattern might be that in the monkey the longer convulsion and respiratory arrest brought about an excessive accumulation of acid metabolites, which produced a momentary peripheral vasodilatation. But during this interval muscular relaxation occurred and respiration was resumed, so that the excessive vasodilator substances would be quickly removed and vasoconstrictor tone would again return in the peripheral vessels. The more extensive duration of the convulsions in the monkeys might account also for the longer time required for the cardiovascular response to return to control levels, as compared with the time required in the dogs.

With respect to the pattern of blood flow and blood pressure response to electroconvulsive stimulation, it would appear that the initial decrease in the tonic phase followed by an increase to a peak elevation during the clonic phase of the convulsion is an accurate account of events, regardless of the species studied or the method of measurement, since this pattern has been observed in rabbits by Schmiterlöw and Silfverskiöld,[4] and by Piette,[5] in dogs by Brown and associates,[1] in monkeys in the present study, and in man by Gibbs and co-workers[6] and others. The secondary decline with a subsequent elevation in both flow and pressure after the convulsion has been observed in man by Silfverskiöld and Åmark[7] and in rabbits by Schmiterlöw and Silfverskiöld.[4]

One of the most important observations in this study on monkeys is that in response to electroconvulsive shock the arterial pressure pattern duplicates the blood flow pattern in time and direction of change. This confirms the results of the

4. Schmiterlöw, C. G., and Silfverskiöld, B. P.: Disturbance of Circulation in Convulsions of the Epileptic Type: Animal Experiments, Acta physiol. scandinav. **6**:187, 1943.

5. Piette, Y.: Motor, Respiratory, Cardiovascular, and Glycemic Changes During Electroshock: Experimental and Clinical Study, Ann. Soc. Sc. méd. nat. Brux. **3**:5, 1950.

6. Gibbs, F. A., and others: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257, 1934.

7. Silfverskiöld, B. P., and Åmark, C.: Disturbance of Circulation in Convulsions of the Epileptic Type: Arterial and Venous Pressure During Electroshock, Acta med. scandinav. **113**: 191, 1943.

previous work on dogs subjected to electroconvulsive shock.[1] The importance of this observation lies in the fact that if arterial pressure measurements are made in man under conditions similar to those of the present study, one may, with greater confidence, make generalizations regarding blood flow events by analyzing the arterial pressure pattern elicited.

The response of the cardiac rate to electroconvulsive shock in the 10 monkeys of this series of experiments was an initial, brief bradycardia in the beginning of the tonic phase, followed by tachycardia for the duration of the convulsion. Subsequent to the convulsion, cardiac arrhythmia was observed, involving extrasystoles and asystoles, which persisted for several minutes after shock. Except for the initial decrease, followed by a marked increase in cardiac rate after the onset of electroconvulsive shock, the cardiac rate is unpredictable and lacks the uniform pattern found for postshock blood flow and blood pressure.

The results from the studies on electroconvulsive shocks in dogs and monkeys offer indirect evidence against the hypothesis that an extensive functional cerebral ischemia is associated with this procedure. In the monkeys the blood flow through the internal carotid artery was increased more than 200% during the convulsion and required approximately 30 minutes to return to control levels of flow. Both the systolic and the diastolic pressure were strikingly elevated during the convulsions and also required several minutes to subside to control levels, thus providing a strong head of pressure to sustain an increased cerebral flow. The changes in cerebral blood flow in the monkeys, as in the dogs, appear to be a passive response to pronounced elevations in systemic blood pressure. The initial decrement in blood flow, blood pressure, and cardiac rate following the onset of electroconvulsive shock was of such a transient nature—one to three seconds—that it was not considered to have therapeutic significance. Whether or not the marked elevations in blood flow, blood pressure, and cardiac rate have therapeutic significance is not yet known.

SUMMARY AND CONCLUSIONS

The immediate effects of electroconvulsive shock on the internal carotid blood flow, arterial pressure, and cardiac rate were recorded in experiments on a series of 10 monkeys under light chloralose anesthesia. The shock stimulus, in terms of milliamperage, voltage, and duration of current, was also recorded.

Blood flow was measured continuously in the internal carotid artery by the use of an electromagnetic blood-flow meter. By the use of a Statham gage-Offner recorder system, blood pressure was measured directly and continuously at the same site as was blood flow. Changes in cardiac rate were obtained from the pressure records.

The initial responses to electroconvulsive shock were convulsions, respiratory arrest, bradycardia, and reduced cerebral blood flow and arterial pressure; the last three responses had a duration of one to three seconds. This initial decrement in blood flow, blood pressure, and cardiac rate was followed by a pronounced increase above control levels, which reached a peak during the clonic phase of the convulsion. Blood flow and arterial pressure reached their highest elevations concomitantly; and then, while the convulsion and respiratory arrest continued, they began to decline. The lowest point of this secondary decline was reached a few

seconds after the end of the convulsion. Blood flow and blood pressure then exhibited a secondary rise, which reached peak elevations one minute after shock. Blood flow and blood pressure then began a gradual decline until, 30 minutes after shock, blood flow and arterial pressure in a majority of the 10 animals had returned to control levels. After the initial decrease and increase following electroconvulsive shock, the cardiac rate exhibited a gradual, but erratic, decline toward control levels; control levels were reached by a majority of the animals within 30 minutes after shock. At the cessation of the seizures the monkeys exhibited a prolonged cardiac arrhythmia, of several minutes' duration.

This study on monkeys supports the conclusions drawn in a previous work on dogs that changes in blood flow in the carotid artery appear to be a passive response to marked changes in arterial pressure. Because of the pronounced elevations which occur in blood flow and arterial pressure during the convulsions in monkeys subjected to electric shock, support is also given to a previous contention that cerebral ischemia resulting from cerebral vasoconstriction is not of functional significance in electroconvulsive shocks.

INCIDENCE OF ALZHEIMER'S DISEASE IN A LARGE MENTAL HOSPITAL

Relation to Senile Psychosis and Psychosis with Cerebral Arteriosclerosis

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SYSTEMATIC histologic studies by means of silver-staining techniques of large numbers of brains from autopsies at St. Elizabeths Hospital have demonstrated the widespread distribution of argyrophilic plaques and neurofibrillary changes in a proportion of persons larger than had been anticipated. The brains of such patients were in general smaller than the average and showed varying degrees of atrophy and mild or advanced ventricular dilatation without obstruction to the flow of cerebrospinal fluid. Sclerotic or atheromatous plaques were often observed in the walls of large vessels, but the vascular changes did not appear to be of sufficient magnitude to account for the clinical picture. Only in rare instances were focal lesions observed in this group.

Many of the patients were above the age limits to which Alzheimer's disease is generally attributed. A large number had entered the hospital at an advanced stage of their illness, when neurologic signs were prominent. The most commonly mentioned manifestations of central nervous system pathology were forced crying and laughing, or emotional lability, forced grasping, pseudobulbar paralysis, and speech disturbances. These appeared late in the disease. The clinical histories were indicative of a long progressive mental deterioration, with no disturbance in the motor sphere in the early phases.

Few articles on Alzheimer's disease have appeared in the literature in recent years, although in previous decades the condition occupied the interest of many neuropathologists. In these early reports two schools of thought emerged: those who believed that Alzheimer's disease was a presenile form of senile dementia with a similar clinicopathologic picture, but one which occurred in an earlier age group and showed more intense histologic changes; and those who arrived at the conclusion that the characteristic microscopic alterations could be the result of etiologic factors other than senility and that many senile persons did not show "senile" plaques or Alzheimer's neurofibrillary changes. Since opinion is apparently still divided as to the classification of Alzheimer's disease, it seemed pertinent, especially in view of the current interest in geriatric problems, to restudy the subject.

METHOD AND MATERIAL

This presentation is based on the histologic study of the brains of 210 patients at St. Elizabeths Hospital. For 100 of these patients the diagnosis was psychosis with cerebral arteriosclerosis, and for 50, senile psychosis; and 60 were chosen from miscellaneous categories. The

From the Blackburn Laboratory, St. Elizabeths Hospital.

clinical notes and postmortem protocols in several thousand autopsies [1] were reviewed, and an attempt was made to correlate the recorded clinical changes with the pathologic alterations. Most of the brains selected were not subjected to exhaustive histologic study. Except in certain instances in which thorough sampling of the brain was carried out, only the region of the left frontal pole was selected for silver studies (Braunmühl stain). If atrophy was more prominent in one or both temporal lobes, as happens not infrequently in Alzheimer's disease,[2] sections were taken from these areas as well. When more detailed investigation was necessary, sampling was made from numerous other cortical and subcortical areas and stained with hematoxylin and eosin, toluidin blue 0, phosphotungstic acid-hematoxylin, and the Weil, Holzer, Davenport or Bodian technique.

Table 1 shows the distribution of patients.

ILLUSTRATIVE CASES

CASE 1.—*History* (obtained from a niece).—The patient was the fifth of six children, two of whom died in infancy. A brother died at the age of 29 of typhoid; a sister, at the age of 50, of coronary thrombosis; another sister, younger, with whom the patient lived, at the age of

TABLE 1.—*Diagnostic Distribution of Patients*

Age on Admission, Yr.	Men			Women		
	Senile Psychosis	Psychosis with Cerebral Arteriosclerosis	Miscellaneous	Senile Psychosis	Psychosis with Cerebral Arteriosclerosis	Miscellaneous
20-29	..	..	2	..	..	3
30-39	..	..	..	..	..	2
40-49	..	2	4	..	1	5
50-59	1	4	5	..	6	14
60-69	2	12	9	4	25	1
70-79	12	11	4	15	20	4
80-89	4	3	1	8	14	6
90-99	3	..	..	1	2	..
Total	22	32	25	28	68	35
	Men 79			Women 131		
	Total 210					

48, of pulmonary thrombosis. The father lived to the age of 81. He was a cartographer and a "devoted patron of music, art, and science." The mother died of pneumonia when the patient was 6 years old.

The patient was considered a sickly, anemic child but was unusually brilliant in school, particularly in mathematics. Upon completing high school, she continued her music studies; she became a concert pianist and played with symphony orchestras. The niece stated that the patient withdrew from public appearances about 1919, after the death of her father, because of her exceedingly shy nature. She had an abnormal attachment to her family and continued to live with her younger sister until the latter's death, in 1936. After this event she kept house for the niece but soon began to manifest signs of inadequacy: She would misplace things, accusing the niece of taking them. She was then 51 years of age. Forgetfulness increased during the following two years. The family physician considered it to be due to high blood pressure and arteriosclerosis. A succession of friends and nurses tried to live with the patient, but she quarreled with each for fancied abuses. The niece would find money concealed in odd places during this period. About 1941 the patient entered a nursing home. She was unsteady in her gait and had trouble in assuming a position. She also had difficulty in dressing herself and even in finding the way to her room. She seemed at first aware of her memory difficulties

1. The large majority of the autopsies were performed by Dr. K. H. Langenstrass.

2. Berlin, L.: Presenile Sclerosis (Alzheimer's Disease) with Features Resembling Pick's Disease, Arch. Neurol. & Psychiat. **61**:369, 1949. Personal observation.

During 1942 and 1943 she was observed to wander about in a bewildered manner, although she remained vaguely pleasant. She had poor muscle coordination. Late in 1943 she had become so feeble that she was confined to bed and had to be spoon-fed.

A convulsion, lasting six minutes, was reported in February, 1944. After this seizure, nursing became more difficult, as she became increasingly noisy. There were no coherent replies to questions. She had occasional convulsive seizures at the nursing home, where she resided for 7½ months, before entering St. Elizabeths Hospital.

Examination.—At the time of admission to St. Elizabeths Hospital, on Nov. 20, 1944, the patient was reported to be completely inaccessible. She lay motionless on the bed and made no sounds except for occasional guttural, incoherent moanings, or bursts of noisy crying without apparent provocation. She was markedly cachetic, and her muscles were atrophic, particularly in the lower limbs. Both arms were strongly flexed; the lower limbs were partially flexed and displayed spasticity when attempts were made to move them passively. The hands were clenched tightly, actively resisting passive motion. The patient displayed numerous tic-like movements of small amplitude throughout the trunk and lower limbs. The pupils were widely dilated and reacted very sluggishly and to a limited degree to light. She was unable to protrude her tongue volitionally (it was beefy red). There appeared to be a response to pinprick, but detailed sensory perception could not be adequately tested. Deep reflexes were hyperactive throughout. Nuchal rigidity was pronounced. The blood pressure was 150/100.

Course.—As noted in this brief account, the physical and mental changes had developed insidiously for seven to eight years, until she became completely bedridden in January, 1944. In the ward she lay helplessly in bed and required much nursing care. At night, unless sedated, she was noisy, disturbing the other patients. It was said that her appetite was good, but spoon feeding was necessary. She could not carry out simple commands. Forced grasping and forced laughing and crying were reported on Dec. 20, 1944. On that date the blood pressure was stated to be 210/135. The results of laboratory tests were within normal limits. The admission diagnosis was psychosis with cerebral arteriosclerosis.

Death occurred on March 3, 1945, after a respiratory infection. The patient was then 60 years old.

Autopsy.—An embolus was present in the right pulmonary artery, completely occluding it. Smaller emboli were found in the vascular tree of each lung.

The brain weighed only 1,050 gm. The cerebral hemispheres showed narrow, firm, normally arranged gyri. The lateral ventricles were greatly dilated, and more than 300 cc. of intracranial fluid was collected during the removal of the brain. No gross changes were observed in the brain stem or cerebellum. The cranial nerves were intact. The large vessels showed only mild atheromatosis. After fixation the atrophy was noted to be more prominent and most intense in the frontal and temporal lobes bilaterally.

Microscopic Study.—Sections were taken from various cortical areas, since the progressive mental deterioration of the patient at a relatively early age and the gross appearance of the brain were suggestive of a degenerative disease of the brain. Additional sections were taken from the basal ganglia, cerebellum, and medulla oblongata. Silver-stained preparations (Braunmühl and Bodian methods) demonstrated numerous argyrophilic plaques and Alzheimer's baskets throughout all cortical areas studied, including the insula. The plaques were most numerous in the second layer and were occasionally observed even in the white matter. The neurofibrillary changes were generally in small and medium-sized nerve cells of the third, fourth, and fifth layers. The large pyramidal cells usually showed normal arrangement of their neurofibrils. Specific stains showed diffuse cellular gliosis. Astrocytosis was most prominent in the molecular layer. Proliferation of microglia in the deeper layers was striking; they resembled the rod-cell type. These changes were more intense in a parasagittal section of the left precentral and postcentral regions than in the premotor area. A few swollen pyramidal cells contained vacuoles. Subcortical myelin was diffusely thinned out. Astrocytosis was observed focally in the thalamus and in periventricular regions. Glia cells were also hyperplastic in the molecular and Purkinje layers of the cerebellum. In the medulla oblongata, both pyramids showed slight diffuse pallor in the Weil preparations.

CASE 2.—*History* (obtained from the patient's brother and sister-in-law, with whom she had made her home for the past 25 years).—The father had committed suicide at the age of 74 because of "prostate trouble." The mother lived to the age of 85; because of renal disease, she had been an invalid for more than 20 years prior to her death, much of the burden of her care falling on the patient. An uncle was in a mental institution for about 1½ years previous to his death, at the age of 60. The nature of his illness was not known.

The patient was described as an extrovert; she had never engaged much in solitary pursuits. She had never married. She had worked for 28 years as a government clerk, retiring in 1946, when there was a force reduction. The informants had noticed, however, at that time that she was "beginning to slip." Shortly before her retirement she sought medical advice because of nervousness, restlessness, and confusion. Her condition was considered due to arteriosclerosis, and custodial care was advised. Her condition gradually declined from that time. She misidentified people, wandered away from home, and displayed increasing difficulty in sleeping, dressing, and feeding herself.

Examination.—The patient, aged 67, was admitted to St. Elizabeths Hospital, on Dec. 30, 1949. She was oriented for person, but not for time, place, and situation. She was restless, appeared mentally confused, and showed obvious memory defects during the admission interview. She was observed to pick continually at her clothes or at nearby objects. Her gait was slow and hesitant, and there was moderate cogwheel rigidity of both arms. The facial expression was blank and staring. The blood pressure was 190/100.

Course.—In the ward she was restrained in a wheel chair part of the time to prevent her from annoying other patients with her restless wandering. She required spoon feeding. She talked incessantly, her speech being incoherent and disconnected. Often she did not understand questions and showed echolalia. On neurologic examination, she displayed hyperactive deep reflexes, particularly in the upper extremities. There were also tremors of the upper extremities, together with some rigidity in passive action. Owing to the patient's inability to cooperate, sensory testing could not be carried out. She walked on a broad base with an unsteady gait. The diagnosis was psychosis with cerebral arteriosclerosis.

On March 26 she fell at her bedside and sustained a fracture of the left femur. The following day she was stuporous, dyspneic, and rigid. The jaw hung open and was closed with difficulty. The pupils were miotic and eccentric and reacted slightly to light. Cataracts obscured the view of the retinas. There were occasional muscle twitchings, and all muscle stretch reflexes were hyperactive. There were bilateral grasp reflexes and aimless groping movements of the arms. The Babinski sign was not elicited. On April 9 she exhibited difficulty in swallowing. Numerous large decubitus ulcers developed. She weakened gradually and died April 25, 1950.

Autopsy.—There were no significant abnormalities in the viscera.

The brain showed mild senile atrophy. No sclerotic changes were noted in the cerebral vessels or in the aorta and its branches. Dissection of the fixed brain confirmed the presence of atrophy and disclosed no focal lesions.

Microscopic Study.—A Braunmühl preparation from the left frontal pole showed many argyrophilic plaques in all cortical layers and a few in the underlying white matter. Alzheimer's neurofibrillary changes were also observed in many nerve cells. Additional sections were therefore taken from other cortical areas and from the left basal ganglia, the pretectal region, and the mesencephalon. The characteristic neurofibrillary changes were present in nerve cells of the insular cortex, other cortical regions, and the claustrum, amygdala, pretectal area, and dorsal tegmental nucleus of Gudden (Gudden's ganglion). This alteration was especially prominent in the amygdala. In the pretectal area some of the nerve cells contained a rounded clump of argyrophilic material in their cytoplasm. Plaques were demonstrated in the insula, amygdala, and claustrum. With the Holzer technique, focal proliferation of astrocytes was observed in the subcortical white matter, basal olfactory regions, hypothalamus, external and extreme capsules, and pulvinar. There was moderate fibrillary gliosis in the periaqueductal region, tectum, and posterior perforated substance. Pallidal vessels had deposits of pseudocalcium in their walls.

CASE 3.—The patient, aged 62, was admitted to St. Elizabeths Hospital on Sept. 5, 1948. No contact could be established with her, as she remained mute to questioning. She was ambulatory and appeared apprehensive during the admission examination. The history was obtained from her sister, with whom she had made her home for some years.

History.—The patient was the youngest of eight siblings, all of whom, except for the informant, were dead. There was no known instance of nervous or mental disease in the family. Her childhood had been happy, and she had enjoyed social activities. She had never married. Her only serious illness was scarlet fever, which left her with impaired hearing. The patient completed high school and then was employed in clerical work for many years. Her last position was that of assistant paymaster for a business firm. Since her hearing difficulty had become progressively worse and she had not adjusted herself to the use of a hearing aid, she had stopped working about 10 years prior to her hospitalization. She was described as being independent and self-reliant.

After the death of her brother, with whom she had made her home, the patient joined the household of her married sister, the informant, in 1941. She did well in the new environment despite being extremely deaf. When her sister became ill, in 1946, the patient entered a nursing home, where at first she was able to care for herself. During the following year she showed progressive deterioration, characterized by memory loss, increasing untidiness, and inability to care for her personal needs. She had to be dressed but slept and ate well. No delusions, hallucinations, or other abnormal mental content was evident, and the patient remained pleasant and agreeable. Her physician believed her to be suffering from senile dementia and recommended hospitalization.

Examination.—The physical findings on admission were essentially without significance. The blood pressure was slightly elevated, being 150/90 mm. of mercury. No pathologic reflexes were noted. Serologic reactions of the blood were negative; other laboratory tests disclosed nothing of significance.

Course.—About a month after her hospitalization she was unable to comply with the simplest requests. When questions were addressed to her in writing, she occasionally looked at them but made no response. It was stated that at times she nodded her head in the affirmative or shook it in negation when asked questions loudly. She held a pen correctly in her hand when it was given her but made no effort to write. The conference arrived at no conclusion, and her condition remained an undiagnosed psychosis.

In the ward she wandered about the halls in a confused manner and at times annoyed the other patients. She was untidy in her habits, and her needs were cared for by the nursing personnel. Occasionally she called out in a loud voice, "You crazy fool"; but for the most part she was mute. She was said to grin in a silly manner. She ate greedily. During her restless wandering she sometimes fell, but incurred no serious injury. In May, 1949, it was reported that she "showed frequent mood swings, crying at one time and laughing uncontrollably at another."

By January, 1950, the patient was restrained in a wheel chair to prevent her wandering about and disturbing the other patients. It was necessary to spoon-feed her and to take her periodically to the toilet. Her appearance was untidy. She mumbled occasionally and smiled intermittently. On Nov. 4, she apparently got out of the restraining sheets and was found on the floor with her nose bleeding and an ecchymosis about her left eye.

On Dec. 19, 1950, she had a convulsion. This was believed to be due to a vascular spasm, as there was no paralysis. The reflexes were brisk and symmetrical. The blood pressure was 112/70, and the temperature was not elevated. On Jan. 15, 1951, when the patient was sent to the medical and surgical service for treatment of a rectal prolapse, an old fracture of the left hip was found on x-ray studies. It was not known just when this was sustained. She was treated with supportive measures, but weakened gradually. Death occurred Feb. 4, 1951, when she was 65.

Autopsy.—Autopsy disclosed arteriosclerotic cardiovascular disease, pulmonary embolism, and cerebral atrophy. The brain weighed 880 gm. The cortical atrophy was most prominent in the frontal and temporal lobes. Two hundred cubic centimeters of intracranial fluid was collected. No focal lesions were palpable. The brain stem was large and in contrast to the small cerebrum. The internal carotid and middle cerebral arteries were sclerotic, but the basilar and vertebral

arteries showed only a trace of atheromatosis. Stripping the leptomeninges from the left cerebral hemisphere prior to dissection of the brain revealed atrophy, even in the parietal and occipital lobes (Fig. 1*A*). Horizontal section showed ventricular dilatation and narrow gyri (Fig. 1*B*). The frontal lobes were short. No focal lesions were found, and the diffuse atrophy was suggestive of Alzheimer's, rather than Pick's, disease.

Microscopic Study.—A section from the left frontal pole stained by Braunmuhl's method confirmed the aforementioned impression. This brain presented probably the most advanced form of Alzheimer's disease in the series. The plaques were scattered thickly throughout the cortex. There was widespread loss of nerve cells, and many of the remaining ones showed typical neurofibrillary changes (Fig. 2*A*). Axis-cylinders were fragmented and tortuous and showed focal thickenings. Additional sections were taken from the temporal lobes, right and left basal ganglia, diencephalon, and mesencephalon. In the atrophic temporal gyri, the white matter was much reduced in amount, but the remaining sheaths were well stained. The degenerative process

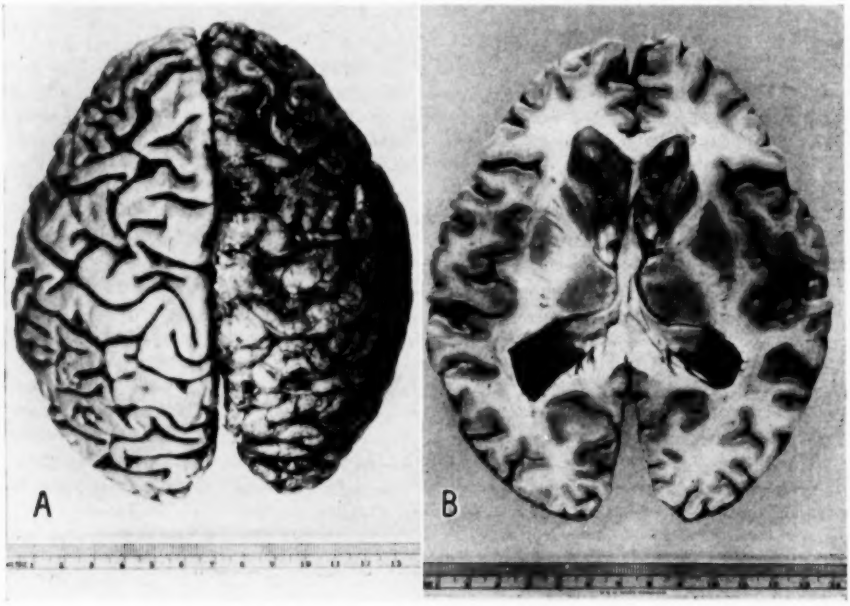

Fig. 1 (Case 3).—Diffuse cerebral atrophy.

in the temporal cortex was as prominent as in the frontal region. In the hippocampus the fascia dentata was intact, and there was only slight loss of nerve cells in the pyramidal layer, although neurofibrillary changes were observed there also. The plaques were visible even in the hematoxylin-eosin preparation; the centers of the plaques with dark nuclei (silver stain) were deeply eosinophilic. Another unusual feature was the definite participation of astrocytes in the plaque formation (Fig. 2*B*). The Holzer stain demonstrated the hyperplasia of astrocytes in the temporal gyri and subcortical nuclei. This was most prominent in the medial nucleus of the thalamus bilaterally (Fig. 3). Many of the nerve cells in this region were swollen, had eccentric nuclei, and contained argyrophilic inclusions in their cytoplasm, while in the insula of the same sections the characteristic neurofibrillary changes were observed. No plaques were encountered in the extreme capsule in the silver-stained slides, but in the Holzer preparation there was a suggestion of such structures. In the midbrain, except for the peduncles, astrocytosis was diffuse. No significant changes were observed in nerve cells at this level. There was no vascular degeneration in any of the sections. A slight lymphocytic infiltration was present in a few dilated perivascular spaces.

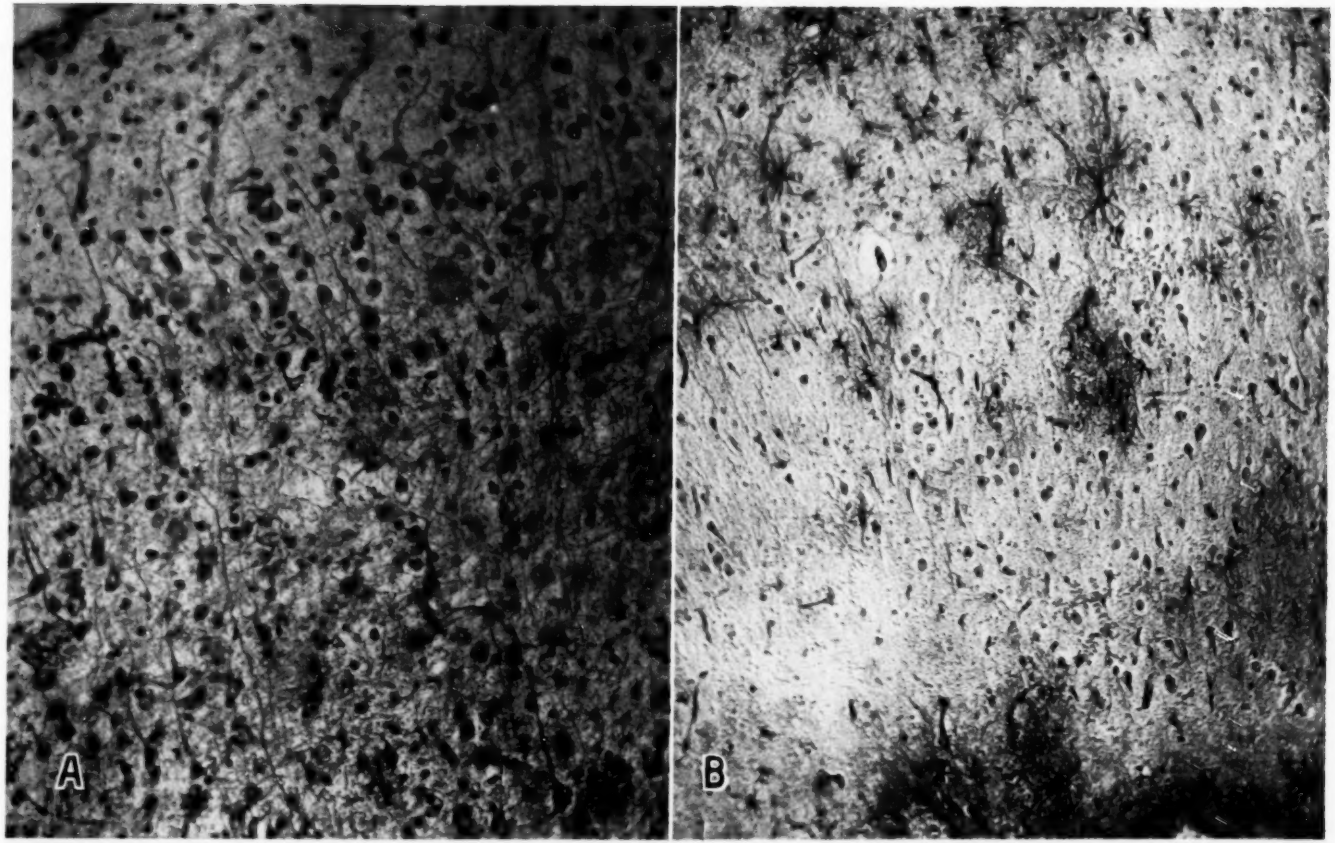

Fig. 2 (Case 3).—*A*, frontal polar cortex, showing plaques and neurofibrillary changes; Braunmühl stain, 8 mm. objective. *B*, hippocampus showing hypertrophied astrocytes in plaque formation; Holzer stain, 16 mm. objective.

CASE 4.—*History.*—The patient, aged 69, was admitted Oct. 6, 1947. An account of her illness was obtained from her husband. The family history was not remarkable. The patient was considered to be a very bright child and had attended college for two years and then taught school for 39 years, retiring six years before hospitalization. She had been married twice; there was one child, now dead, from her first marriage. She had apparently been well most of her life, the only known childhood disease being diphtheria. In 1943 she fell and broke her arm. Her husband believed that her memory gradually failed from that time, becoming progressively worse during the past year. He had found it necessary to assume all home responsibilities. She would remain quiet until about midnight, when she would become restless and talk for hours.

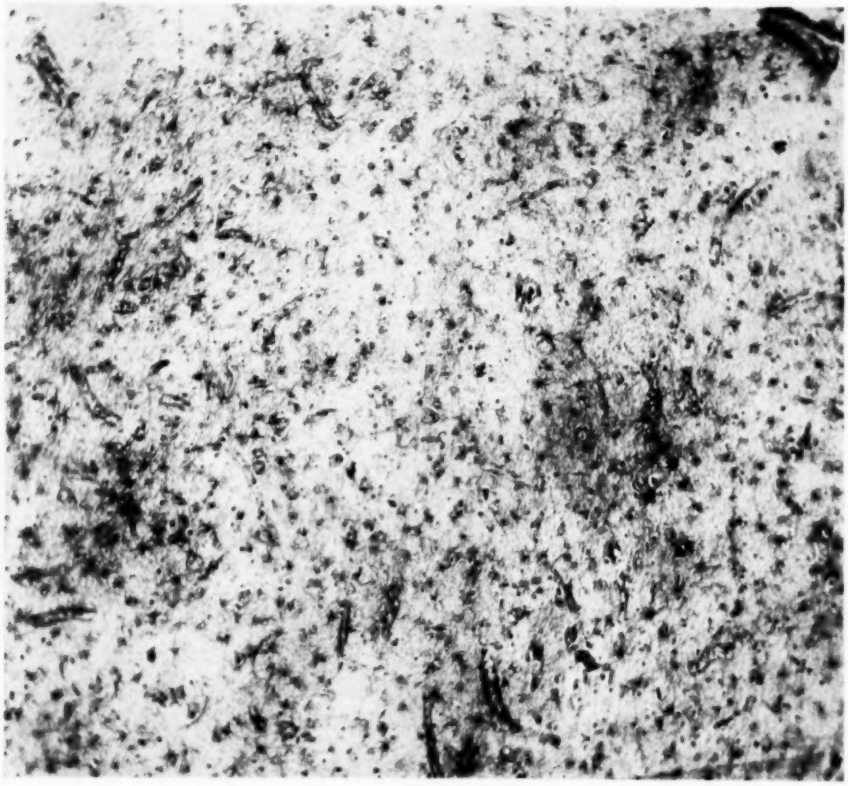

Fig. 3 (Case 3).—Astrocytosis of the thalamus; Holzer stain, 16 mm. objective.

Examination.—She was able to give her name at the initial interview, but when asked her age replied, "I don't know my age. I knew it until yesterday, but my name and age left me yesterday." She rambled on aimlessly and once burst out explosively, "Just today I went perfectly crazy." She was unable to state whether she had any siblings but knew she had a husband. She was friendly except during the physical examination, when she threatened to strike the examiner if she was hurt. The examination was considered unsatisfactory but apparently disclosed nothing significant.

Laboratory tests shortly after the patient's admission showed a strongly positive serologic reaction of the blood for syphilis, but the serologic response of the cerebrospinal fluid was negative. The blood pressure was not elevated.

Diagnosis.—The diagnosis was senile psychosis, simple deterioration, with arteriosclerosis and syphilis.

Course.—In the ward she was restless in spite of her feebleness, and frequent falls were reported. She had a friendly manner and would comment on how nice the women physicians and nurses looked. Generally, however, her long, rambling conversations were irrelevant, and her loud voice would disturb the other patients. It became necessary to restrain her in a wheel chair to prevent her from falling and injuring herself. In September, 1948, she was said to show "an almost constant level of purposeless activity." She was then completely disoriented; she was untidy, soiled herself, and was completely dependent on the nursing staff. In the spring of 1949 she was treated for pinworm infection. About a year later bilateral otitis media and nasopharyngitis developed. There was a progressive decline in her condition, and she died on April 1, 1950, at the age of 72.

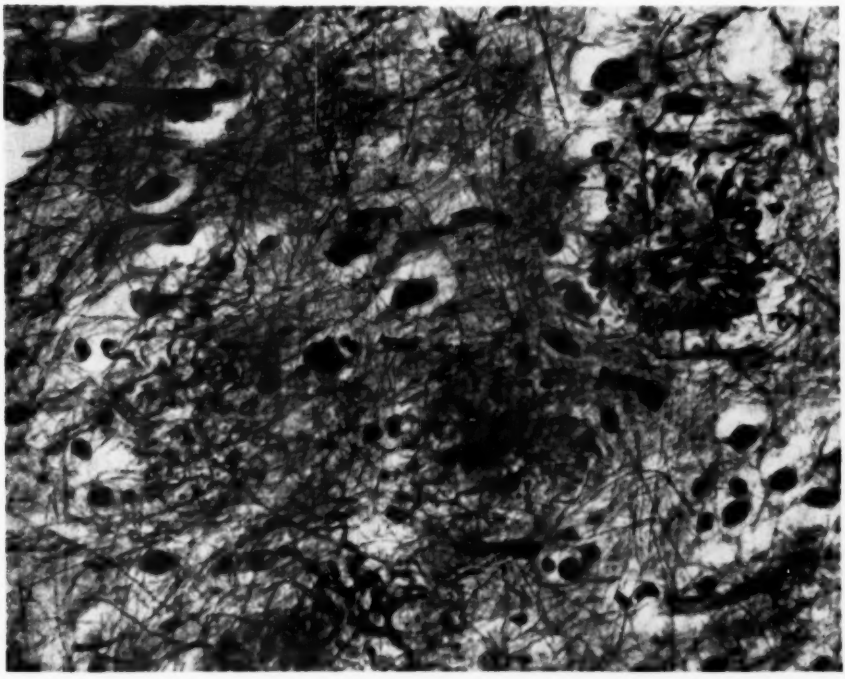

Fig. 4 (Case 4).—Frontal polar cortex, showing plaque structure; Braunmuhl stain, 4 mm. objective.

Autopsy.—Postmortem study disclosed chronic valvular heart disease, purulent polysinusitis, and pleural empyema.

The brain, which weighed 1,130 gm., showed only slight focal atrophy of the left temporal pole. The large arteries were thin-walled and showed scattered atheromatous patches. Examination of the brain after fixation revealed atrophy in the region of the frontal poles. The ventricular system was moderately dilated. No focal lesions were found.

Microscopic Observations.—The numerous argyrophilic plaques in the cortex were exceptionally well defined in the Braunmuhl preparations. Some had large dark central nuclei; others were composed of thickened fragmented fibers with bulbar endings (Fig. 4). In some areas plaques were closely spaced, forming a cluster; in other regions they were more widely scattered. There were relatively few instances of Alzheimer's neurofibrillary changes. Projection bundles of axis-cylinders were distinct, and in general cortical architecture was well preserved.

CASE 5.—The patient, aged 54, was admitted to St. Elizabeths Hospital Oct. 10, 1946. He had graduated in law from a well-known university, where he did exceptionally well in mathematics. After passing the bar examinations and practicing law for a few years, he worked at an astronomical observatory as a mathematician for approximately 11 years. He also did editorial writing and worked as a high school teacher and tutor at various times. His wife, from whom he had been separated for several years, supplied the information that he was a "periodic drunkard" and that she had supported him for many years.

On admission the patient's replies to questions were considered unreliable. For example, he stated that he was not married and was concerned over the health of his mother, who had actually died about 20 years before. He was pleasant, cooperative, and polite, even unctuous, but was disoriented for time and place. He was unable to state the events leading to his hospitalization at Gallinger Municipal Hospital for mental observation; the record from this institution indicated that he showed gross memory failure, disorientation, and confusion. The only known familial determinant was the history that a cousin of his, a high-ranking officer in World War I, had been a patient at this hospital.

Examination.—At the admission conference it was noted that the patient's appearance and manner suggested the possibility of an old alcoholism. The diagnosis, however, was psychosis with cerebral arteriosclerosis. The blood pressure was 120/70. The deep reflexes were hyperactive.

Course.—The patient remained neat and tidy, participating in social activities, but refused to do any ward work. He spent most of his time reading, but the subject matter was not stated. There was a marked deterioration from his previous high intellectual level. Although the patient himself insisted that his memory was good, most of the notes throughout the years refer to his poor memory, especially for recent occurrences and "everyday affairs." In September, 1947, it was stated that he sometimes forgot the location of his bed. He was able to carry on normal coherent conversations and adapted himself well to hospital life.

In February, 1948, x-ray studies revealed that the patient had a neoplastic process of the descending colon. Intestinal obstruction developed, and a cecostomy was performed Feb. 16. Convalescence was poor, and he died 10 days later, after a gastric hemorrhage.

Autopsy.—The cause of death was carcinoma of the rectum, intestinal obstruction, and massive pulmonary edema. (It is of interest that seven members of his family were known to have died of cancer.)

The brain weighed 1,440 gm. and showed no focal lesions, either externally or on section. The large arteries at the base were narrow and thin-walled, almost completely transparent, and practically free from lesions. Histologic study showed slight increase of reticulum in the walls of small vessels. The cytoarchitecture was well preserved, and nerve cells showed no significant changes. There was no evidence of a degenerative brain disease.

CASE 6.—*History.*—The patient, an enfeebled old Negro who was said to be 92 at the time of his admission, entered the hospital on May 29, 1947. He had never attended school. He was oriented for person and knew that he had come from Gallinger Municipal Hospital. He was said to have come to Washington only five years previously, making his home with an informant, who stated that the patient received an old-age pension. He never went out and never received visitors. About a month before his hospitalization, the informant noted that the patient "talked foolishly." He was observed to talk to himself and reminisce about long past events. One night the patient attempted to get to his trunk to obtain "razors and an old shotgun," stating that he would kill himself; his landlord therefore had him hospitalized.

At the admission interview he was pleasant and attempted to answer all questions, although some of the replies were "contradictory." He knew the date and place of his birth but could not recall the names of his two wives.

In spite of his feebleness, he was able to care for his own needs and maintain a fairly neat appearance. He took little interest in ward activities but liked to talk about his childhood days in slavery. He said that his father was a slave but his mother was a free woman. He was disoriented for time but knew where he was. At times he was reported to be relevant and clear in his conversation. The physical findings were not significant. The blood pressure was reported as 118/60. The neurologic status showed no marked abnormalities. The serologic reaction of

the blood was negative. The diagnosis was senile psychosis, simple type. Since he made an excellent hospital adjustment in spite of his memory defects, he was soon given ground parole privileges. He also improved physically, and it was decided to transfer him to the Home for the Aged, when he had onset of jaundice. He died about three months later. Carcinoma of the pancreas had been suspected, but no malignant growth was found in any of the viscera. The liver showed mild biliary cirrhosis. The aorta and coronary arteries were described as being remarkably well preserved. The kidneys showed thick-walled arteries and small retention cysts. The cause of death was given as arteriosclerosis and uremia.

The brain, which weighed 1,100 gm., was ischemic and edematous. The cerebral arteries were hypoplastic and showed a few small yellow plaques in their walls. Slight ventricular dilatation was found on dessection of the brain. A very small cystic infarct, 2 mm. in diameter, was observed in the middle of the right centrum semiovale. Sections stained by Braunmühl's method showed no argyrophilic plaques or Alzheimer baskets. However, the architecture was not well preserved, and there was loss of nerve cells. Axis-cylinders were occasionally fragmented. The marginal glial layer was thickened. The blood vessels showed no degenerative changes.

COMMENT

The clinical picture that emerged as a concomitant of widespread formation of argyrophilic plaques and neurofibrillary changes was remarkably consistent and characteristic throughout the series. These changes were representative of progressive mental deterioration for several years prior to hospitalization. At the time of admission the patients were seldom able to furnish any coherent or reliable information about themselves. The profound personality changes, as described by their relatives, were insidious in onset. Generally the patients with the longest prehospitalization period were housewives who, although becoming gradually less competent to perform their household tasks, had been cared for in the home as long as this was possible. In addition to showing failing memory and confusion in recognizing objects in their environment and their normal uses, the patients became progressively untidy and frequently incontinent of urine and feces. This was generally in contrast to their previous neatness, or even meticulousness. An oft-repeated history was that the patient would turn on the gas and forget to light it or that she (or he) would misplace personal belongings (money or jewelry) and accuse the relatives of stealing them. These objects were never found. More characteristic, however, was the tendency to wander away from home, frequently into neighbors' dwellings, or to become "lost" on the streets. In their homes, they prowled the house at night; after hospitalization they wandered aimlessly and ceaselessly in the ward, as though searching for something, and frequently tried all doors. They could not find their way to the dining hall or bathroom. If confined to bed as they became more feeble, they picked aimlessly at the clothing or coverings or at objects in their vicinity. Frequent falls were reported in the transition period from the stage of excessive motor activity until restraint in wheel chair or bed became necessary. In the final stage spoon feeding was required, and in the terminal period difficulty in swallowing was often observed. Unless death occurred early in the disease process, usually from a respiratory infection, the terminal phase was a completely vegetative existence, where all needs were provided for by the nursing staff.

In the language sphere, the difficulty was usually first in the forms of expression; if the parietal association areas were extensively involved, aphasia was noted. In the terminal stages the patient was usually mute.

This pattern occurred over and over again, with only minor variations. It never failed to be present when pronounced cortical degeneration with plaques and neurofibrillary changes was the most prominent feature. The terminal clinical picture depended, of course, on whether the patient died at an early stage, of neoplastic, cardiovascular, or other cause. The initial phase, as seen by the admission staff, depended on how long the relatives had been able to afford private nursing care or on how long they could bear the burden themselves. The severity of the process had no relation to the age of onset of symptoms.

Senile Psychosis.—Of the 50 patients with this diagnosis selected for inclusion in this report, the youngest was admitted to the hospital at the age of 58 and died at the age of 76; the oldest was admitted at the age of 94. More than one-half the patients (*27*) were in the eighth decade. In 32 brains argyrophilic plaques were found; *22* of these showed neurofibrillary changes of the Alzheimer type as well. Twenty of the *22* patients (5 men and 15 women) showed the clinicopathologic combination described above. In the brains of the other two patients plaques and cell changes were rare or moderate in distribution; one of these patients, a woman of 80, suffered from hypertension and showed gross and microscopic evidence of cerebrovascular disease, with a small cystic infarct in the right frontal lobe. Of the 10 patients in whose brains plaques were observed but no neurofibrillary changes, 4 showed few, if any, of the "typical" clinical traits. One of these patients had been in the hospital previously for treatment of dementia paralytica. His brain showed an old subdural hematoma. The brain of another presented many infarcts. Three with plaques only displayed restless wandering and untidiness. The histories of the others showed marked deviations from what is described, and is considered, as the "characteristic" picture in this communication.

Sclerotic changes in large vessels were present in 38 brains; 17 showed microscopic evidence of vascular disease. Of the latter group (vascular degeneration at a microscopic level), eight showed characteristic histologic changes of Alzheimer's disease, or plaques only. Small infarcts, believed to have no significant effects on the patient's overt behavior, were found in rare instances.

Since the statement is not infrequently made that plaques and neurofibrillary changes are the usual concomitant of old age,[3] the changes in the oldest patients—seven men and nine women—will be briefly summarized. In view of the advanced age of the oldest patient, 96 at death, it is perhaps surprising that argyrophilic plaques and neurofibrillary changes were relatively rare. The cortical architecture showed minor changes. The walls of a number of small blood vessels had increased reticulum. The patient was in the hospital less than two years, but the daughter stated that mental deterioration had been present for at least two years prior to hospitalization. She stated that he had a tendency to wander away from home and annoy the neighbors. At the hospital, he was untidy, required much nursing care, and was very confused and disoriented. The other three patients who were in the 90's on admission showed only a few plaques, or none, and no neurofibrillary changes. Of the patients (12) in the ninth decade of life, 2 showed both plaques and characteristic cell changes, and each of the latter had a "typical" clinical history of progressive social adaptation at a lower level. One of these patients had shown

3. Simchowicz, T.: Sur la signification des plaques séniles et sur la formule sénile de l'écorce cérébrale, Rev. neurol. **31**:221, 1924. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous Systems, Ed. 3, Chicago, the Author, 1948. Freeman, W.: Neuropathology, Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1933.

progressive symptoms since the age of 73; after being in private nursing homes until her care became too difficult, she entered St. Elizabeths Hospital, at the age of 81, and died two years later. The other patient, also a woman, was in the hospital six years, dying at the age of 90. This woman's sister is also a patient, but at the time of writing is still alive. Five patients had neither plaques nor cell changes; the others had plaques, in varying amounts, and no specific cell changes. One elderly woman, admitted at the age of 82, had a history, as given by her son, which was considered suggestive of Alzheimer's disease. Repeated silver staining of sections of the brain revealed only evidence of arteriosclerosis. However, she had been in this country only a few years, coming from Armenia to join her son, and spoke very little English, as well as having only limited ability to understand the language. She was also blind and partially deaf, so that a true evaluation of the mental syndrome was difficult of accomplishment.

One other case may be briefly mentioned. The patient, a clergyman for many years, was admitted at the age of 92 and died two weeks later, as the result of a coronary occlusion. His daughters set the date of onset of his mental changes about six years prior to this, when he married a woman of 24. On admission, he was disoriented, his speech irrelevant, and he could give no coherent history. The blood pressure was somewhat elevated, being 160/60 mm. Hg. He picked restlessly at the bed covers during the interview. Autopsy revealed generalized arteriosclerosis, but the cerebral vessels were surprisingly well preserved. Histologically, there was likewise no evidence of vascular disease, although numerous infarcts were observed in both cerebral hemispheres, of cortical and subcortical occurrence. There were very few argyrophilic plaques and no demonstrable neurofibrillary changes.

Psychosis with Cerebral Arteriosclerosis.—Of the 100 patients with this diagnosis, 63 showed gross vascular degeneration. Microscopically, thickening of walls of small vessels was noted in 24 brains, although the sampling in many cases was not extensive. Infarcts were found in 10 brains. A high blood pressure was reported in 22 patients. It should be stated, however, that when patients with this diagnosis showed obvious neurologic symptoms of brain pathology, and infarcts were found at autopsy or on brain dissection to explain these deficits, sections were not selected for inclusion in this series unless other clinical signs indicated the presence of a degenerative cerebral process or unless they were desired for comparative purposes. This should not be taken to mean that hypertension and Alzheimer's disease are mutually exclusive. The two conditions were found to exist together in seven patients of the series. Two other hypertensive patients showed argyrophilic plaques only. Infarcts were found in six patients, five of whom showed plaques also in varying amounts. The sixth, a woman of 68, had a history of memory loss and untidiness and of becoming lost on the streets during the year prior to admission. Death occurred five months after hospitalization. The brain showed hypertensive encephalopathy (the blood pressure had been recorded as 230/120) with numerous recent hemorrhages and hemorrhagic infarcts bilaterally. Many argyrophilic plaques, as well as neurofibrillary changes, were found throughout the cerebral cortex.

In a patient with a markedly atrophic brain plaques and neurofibrillary changes were observed in the hippocampus, while in other areas of the cerebrum the classic changes of Pick's disease were seen (Case 2[4]). A somewhat similar condition was

4. Neumann, M. A.: Pick's Disease, J. Neuropath. & Exper. Neurol. **8**:255, 1949.

found recently in a patient with pronounced atrophy of the temporal lobes; a moderate number of argyrophilic plaques were observed in the region of the frontal pole, while in the sclerotic temporal lobes the cortical devastation, rounded argyrophilic inclusions in swollen nerve cells, and extensive astrocytosis were indicative of Pick's lobar atrophy. A third patient of this series, with focal atrophy of the brain and clinical signs of pseudobulbar paralysis, presented the changes of Pick's disease type II.[4]

Three other patients presented the symptom of pseudobulbar paralysis. One showed minute cortical infarcts, as well as argyrophilic plaques (no neurofibrillary changes), and dystrophy of the descending cortical pathways. This picture was similar to that in a case reported by Barrett in 1913.[5] A second subject, with left hemiplegia, had multiple infarcts in the brain and gross and microscopic arteriosclerosis. A third patient had no evidence of vascular degeneration but showed typical histologic changes of Alzheimer's disease. It is of interest that this patient represents the only known instance of unequivocal familial incidence of the disease in our series. This woman's younger sister was admitted to the hospital only five days after her own hospitalization. Shortly after this time convulsions were reported. Her mental changes were difficult to evaluate, and her psychosis remained undiagnosed (included in the miscellaneous group). For a few other patients there were references in the histories that one or more relatives had shown similar mental changes prior to death, though not in this hospital, but no microscopic findings were reported for any of them.[6]

The ages on admission of the patients with the diagnosis of psychosis with cerebral arteriosclerosis ranged from 45 to 90. The two oldest, both women, died at the ages of 94 and 95 respectively. The brains of both showed only a few scattered "senile" plaques and no neurofibrillary changes. One presented arteriosclerosis at a microscopic level; the other, who was reported as alert and cooperative, showed both gross and microscopic vascular degeneration but no lesions. Her blood pressure had been elevated.

The duration of symptoms in the patients with demonstrated Alzheimer's change was in almost all instances much longer than in patients without this cerebral alteration. While sometimes the relatives stated only that the patient had shown progressive mental deterioration for "many years," a fairly specific time of onset for the intellectual degeneration could be reported in most instances, six to eight years prior to admission being not uncommon. For two patients the duration of the illness was 12 and 16 years respectively. The tendency to wander away from home and become lost, as well as the fear that the patient might be injured as a result of his mental incapacity, was frequently the precipitating factor in hospitalization.

5. Barrett, A. M.: A Case of Alzheimer's Disease with Unusual Neurological Disturbances, J. Nerv. & Ment. Dis. **40**:361, 1913.

6. Since this series was completed, another familial case has been noted. A man of 79 was admitted to the hospital Oct. 24, 1951, and died two months later, of uremia. As he was ill much of the time, he was not presented at a formal admission conference. His prehospitalization history conformed to the "classic" picture of Alzheimer's disease. Very many argyrophilic plaques were scattered thickly throughout the cortex of the frontal pole, but neurofibrillary changes were not prominent. Studies on other areas of the brain are now in progress.

This man's brother was also a patient at St. Elizabeths Hospital from May 8, 1940, until his death, April 28, 1944, from lobar pneumonia, at the age of 76. A diagnosis of psychosis with cerebral arteriosclerosis was made. The cortex showed many typical Alzheimer baskets and fairly numerous argyrophilic plaques.

Altogether, 68 patients with the diagnosis of psychosis with cerebral arteriosclerosis showed argyrophilic plaques in considerable numbers. Forty-nine of these patients showed neurofibrillary changes as a prominent feature. Seven additional subjects presented a few scattered plaques, considered of no significance in the patient's mental condition. When the history was adequate, almost all the patients with unequivocal pathologic changes of Alzheimer's disease (49%) were found, when all the clinical notes were reviewed, to have the "typical" personality and behavior changes as well. This was true regardless of the age on admission or at death.

Miscellaneous Group.—Table 2 shows the categories from which the miscellaneous group was selected. The ages of the 25 men and 35 women on admission

TABLE 2.—*Diagnostic Categories in Miscellaneous Group*

Conference Diagnosis	No. of Patients
Dementia praecox	12
Paranoid state	2
Involutional melancholia	1
Dementia paralytica	3
Manic-depressive psychosis	2
Alcoholic psychosis	5
Post-traumatic psychosis	2
Psychosis with other disturbances of circulation (hypertension)	1
Mental deficiency without psychosis	1
Epilepsy	1
Condition undiagnosed; convulsions	2
Alzheimer's disease	2
Psychosis with cerebral atrophy—Pick's disease	3
Psychosis with unknown or hereditary factors, associated with organic disease	1
No diagnosis; death soon after admission	18
No diagnosis, longer residence	3
No psychosis; patient mentally subnormal	1
Total	60

ranged from 22 to 88; the ages at death, from 40 to 98. The 18 patients who died shortly after their hospitalization, without being presented at a formal admission conference, were selected because of their age (within either the senile or the presenile limits) or because their prehospitalization history was strongly suggestive of a cerebral degenerative disease. This diagnosis proved correct for five patients. Four others showed plaques only. Fourteen had sclerotic changes in large vessels, and 4, microscopic evidence of arterial degeneration. For three other patients, with a longer hospitalization period—19 years, 7 months, and 2 years respectively—the disease remained undiagnosed. The patient with the longest residence had an equivocal history. The brain showed multiple small infarcts, vascular disease at gross and microscopic levels, many argyrophilic plaques, and, in a few instances, neurofibrillary changes. The other two patients showed the characteristic progessive mental deterioration of Alzheimer's disease, corroborated by histologic investigation.

Of interest are the three patients with the diagnosis of psychosis with cerebral atrophy, probably Pick's disease, and the two who received the diagnosis of Alzheimer's disease. One patient in each group showed the changes of Pick's disease (Type II), and their cases have been reported in detail.[4] The other four presented no evidence of a degenerative brain disease, and even showed a healthy vascular system. In fact, the brains of two patients, from which extensive sampling was

made, appeared essentially normal. The history of neither patient corresponded to that described as "characteristic" of Alzheimer's or Pick's disease.

A patient with a diagnosis of dementia paralytica and a history suggestive of Alzheimer's disease showed marked atrophy of both temporal lobes. No plaques were found on repeated trials with silver techniques, but a number of nerve cells in the pyramidal layer of the hippocampus presented well-defined neurofibrillary changes.

Several of the patients with schizophrenic reaction patterns were admitted in early adult life. One woman died at the age of 82, after a hospitalization of 46 years. In later years she exhibited hypertension, as well as personality changes suggestive of a degenerative condition of the brain.[7] The cerebral sections showed changes characteristic of Alzheimer's disease. Another patient in this group died at the age of 98, after a hospital residence of 56 years. The brain was grossly atrophic, but Alzheimer's changes could not be demonstrated. Another patient, of 80 (with 31 years' residence), showed increased deterioration and untidiness in her later years, but the sections likewise revealed neither plaques nor neurofibrillary changes. This patient had a large glioblastoma multiforme of the cerebellum, which apparently gave rise to neurologic signs only in the last five months of her life.

One other patient in the miscellaneous group deserves specific mention. This woman, admitted at the age of 45, exhibited no psychotic content and only slight questionable mental deficiency. About four months prior to admission she had suffered paralysis of the left arm, with only slight recovery. Approximately three months later her relatives stated that she had had a convulsion. No subsequent seizures were described. At the admission conference no conclusion was reached as to her mental status. She showed a gradual physical decline and died 16 months after hospitalization, subsequent to a massive cerebral hemorrhage in the left parietal lobe. There was never any evidence of hypertension, and the large cerebral vessels were free from sclerosis; but, interestingly, pronounced and widespread endarteritis was present throughout the brain. In this patient, the advanced degenerative changes in the small cerebral vessels were among the most prominent observed at this hospital. An old hemorrhagic infarct was found in the arm region of the right precentral and postcentral gyri. In an endeavor to trace the origin of the patient's difficulties, the Dieterle stain for spirochetes was carried out on several cortical areas. Surprisingly, large numbers of argyrophilic plaques were demonstrated throughout the cortex with this silver technique. No instance of neurofibrillary change was observed with the Braunmühl method. The plaques were larger and more atypical than those ordinarily observed in Alzheimer's disease.

In summary, 25 patients showed the presence of argyrophilic plaques in the brain sections; 14 of these had neurofibrillary changes also. In the patients with both changes for whom the histories were adequate, the progressive mental deterioration was prominent over a period of years. Several of the patients with plaques only showed many elements of the "classic" symptomatology. The one patient with neurofibrillary changes in the hippocampal region, with no plaques, had a history suggestive of degenerative brain disease, but the case was complicated by serologic signs suggestive of dementia paralytica. Thirty patients had gross evidence of arterial disease, and 16 showed vascular changes on the microscopic level. The latter lesions were not always in brains with sclerotic changes in the large vessels.

7. The case was called to our attention by Dr. G. D. Weickhardt.

COMMENT AND REVIEW OF THE LITERATURE

Alzheimer presented his initial case in 1906.[8] His patient showed her primary symptoms at the age of 51 and died 4½ years later. It should be noted, however, that, although Alzheimer was the first to observe the combination of plaques and neurofibrillary changes with the curious clinical picture, the miliary plaques had been described as early as 1892 by Block and Marinesco.[9] Their patient was an elderly epileptic. The next two reported observations of plaques (Redlich[9] and Léri[9]) were also in elderly persons who had epilepic seizures.

Using the newly developed silver techniques, Alzheimer[10] subsequently studied large numbers of brains and found similar nerve-cell alterations in many instances (1911). Perusini[9] described four cases with similar clinical and histologic changes (1909) and gave the name of Alzheimer to the disease process.

These studies were the impetus to many investigations throughout the next 30 years. It was soon proved that the lesions were in no way related to epilepsy, but could be commonly demonstrated in the brains of elderly persons who were psychotic. Simchowicz,[3] who carried out extensive researches on the pathologic anatomy of senile dementia in Alzheimer's laboratory from 1907 to 1910, apparently initiated the idea that plaques were characteristic and typical of the senile cortex, since he found these lesions also in the brains of "normal" old people. However, in subsequent studies reported by other observers, plaques were also demonstrated in the brains of relatively young persons, who showed the "classic" clinical picture. Barrett's patient, for example, manifested her symptoms at the age of 33, death occurring at the age of 37.[5] Plaques and neurofibrillary changes were found in all cortical areas, and plaques alone, in the diencephalon, corpora striata, and claustrum. There was striking degeneration of the pyramidal tracts from the peduncles to the lower sacral portion of the cord.

A patient described by Malamud and Löwenberg[11] is probably one of the youngest on record to show the characteristic histologic changes. These were prominent, although the patient was only 23 at the time of death. The authors agreed that "by retaining the concept of precocious senility as causative of the changes in Alzheimer's disease, one stated nothing definite about them," since the process of senility is still little understood. Löwenberg and Rothschild[12] pursued this theme and concluded "there were a number of observations which tended to cast doubt on the validity of the generally accepted theory that Alzheimer's disease is an atypical form of senile dementia," and that, in fact, it is really a syndrome with a multiplicity of etiologic factors.

Ferraro and Jervis,[13] likewise, described two cases of progressive mental deterioration, with onset at the unusually early age of 33 and 38 respectively. Both

8. Alzheimer, A.: Über eine eigenartige Erkrankung der Hirnrinde, Centralbl. Nervenh. u. Psychiat. **18**:177, 1907.

9. Cited by Simchowicz.[3]

10. Alzheimer, A.: Über eigenartige Krankheitsfälle des späteren Alters, Ztschr. ges. Neurol. u. Psychiat. **4**:356-538, 1910-1911.

11. Malamud, W., and Löwenberg, K.: Alzheimer's Disease: A Contribution to Its Etiology and Classification, Arch. Neurol. & Psychiat. **21**:805, 1929.

12. Löwenberg, K., and Rothschild, D.: Alzheimer's Disease: Its Occurrence on the Basis of a Variety of Etiologic Factors, Am. J. Psychiat. **11**:269, 1931.

13. Ferraro, A., and Jervis, G. A.: Alzheimer's Disease: An Attempt at Establishing the Adult Type of the Disease, Psychiatric Quart. **15**:3, 1941.

patients showed the classic clinicopathologic picture. The authors cited five other cases in which the onset of the disease was below the age of 40 (28 to 39 years) and postulated that one should refer to the disease in these seven cases as an adult form. They agreed with earlier observers that any discussion as to whether Alzheimer's disease is closely related to, or independent of, senility is of little significance if the nature of the process of senescence is not known, and that a variety of factors independent of senile conditions could play a role in the etiology.

Grünthal,[14] too, recognizing the occurrence of plaques and neurofibrillary changes in rather young persons (such as Barrett's), suggested that these histologic changes might be due not only to the aging process, but also to other factors. He observed, as did Braunmühl some years later, that there is a much wider variety of psychiatric syndromes than there are possible tissue reactions of the brain.

Braunmühl[15] was convinced that Alzheimer's disease is not an early form of senile dementia, but a specific disease entity. Like Pick's disease, it has a wide span for age of onset. Early forms may appear in the third decade of life; late forms, in the seventh. He brought out clearly that all aspects of the problem are not yet understood, and cited the case of a 75-year-old man who remained mentally clear until his death, and whose brain yet showed large numbers of "senile" plaques throughout the cortex. Braunmühl recognized that there are instances of Alzheimer's disease with many plaques and without neurofibrillary changes, and those in which the reverse is true. He therefore concluded that there was no specificity as to the histopathologic process.

Leavitt and Lewey[16] also concluded that the entire clinicopathologic syndrome should be designated as Alzheimer's disease, regardless of the precise time of life in which the condition becomes manifest.

Rothschild contributed studies on Alzheimer's disease and arteriosclerotic and senile dementias[17] and noted the difficulty in distinguishing the last two conditions clinically. He recognized that the tissue reactions of Alzheimer's disease may be the result of factors other than "senility" and that certain senile patients with psychosis had these histologic changes, while others did not. In his discussion of the arteriosclerotic psychoses,[17c] he made the challenging observation that the discrepancies between anatomic lesions and the degree of intellectual impairment might be based on the difference in capacity of persons to compensate for damage to the brain. He cited instances to illustrate that cerebral lesions do not inevitably produce psychotic manifestations and that, in fact, in many cases the psychosis could not be adequately explained on anatomic considerations alone. To interpret this seeming paradox, Rothschild suggested that the qualities of the living patient are an important factor in the origin of the mental disturbance.

14. Grünthal, E.: Die pathologische Anatomie der senilen Demenz und der Alzheimerschen Krankheit, in Handbuch der Geisteskrankheiten, Spec. Pt. 7, Berlin, Springer-Verlag, 1930, p. 638.

15. von Braunmühl, A.: Die psychischen Störungen des Rückbildungsalters: Anatomischer Teil, Ztschr. ges. Neurol. u. Psychiat. **167**:78, 1939.

16. Leavitt, F. H., and Lewey, F. H.: Alzheimer's Disease Followed by Paralysis Agitans: Case Report, Psychiatric Quart. **19**:26, 1945.

17. (*a*) Rothschild, D., and Kasanin, J.: Clinicopathologic Study of Alzheimer's Disease: Relationship to Senile Conditions, Arch. Neurol. & Psychiat. **36**:293, 1936. (*b*) Rothschild, D.: Pathologic Changes in Senile Psychoses and Their Psychobiologic Significance, Am. J. Psychiat. **93**:757, 1937; (*c*) Neuropathologic Changes in Arteriosclerotic Psychosis and Their Psychiatric Significance, Arch. Neurol. & Psychiat. **48**:417, 1942.

Wertham [18] noted the same discrepancy in his discussion of cerebral arteriosclerosis. He pointed out that extensive lesions due to vascular disease may occur in the brains of persons who show no sign of dementia during life and stated that there is no clear-cut histologic difference between the brains of patients with severe mental symptoms and those of patients without.

Our co-workers and we [19] have confirmed this observation in examination of a number of brains from the United States Naval Hospital at Bethesda, Md. Many of the brains showed prominent arteriosclerosis, much more than has been observed in cases at St. Elizabeths Hospital. The brains were frequently also damaged by the presence of numerous infarcts, of various ages. While many of the patients had a history of cerebrovascular disease of long standing—a few months to as long as 12 years—it is of interest that they were not placed in a psychiatric institution, but were cared for in their homes or transiently in a general naval hospital, although usually in the neurologic services.

Critchley [20] thoroughly reviewed the problems of senility as discussed in the existing literature in two articles published in 1929 and 1931. He pointed out the diagnostic difficulties and the inconsistencies of the pathologic findings. He suggested that aged persons whose brains are free from plaques may well fall into "a psychological category of their own."

A more recent review appeared in 1944, in which Mayer-Gross [21] summarized the literature on arteriosclerotic, senile, and presenile psychoses. He cited the interesting theory of Diethelm and Rockwell that aging frequently "unveils" constitutional personality traits. Greenfield's proposal to classify the arteriosclerotic psychoses on the basis of pathological findings, and that of McNememy, who made a similar suggestion for the presenile group, are also presented.

It is well recognized that there are several types of elderly patients in psychiatric hospitals, exclusive of those with definite focal neurologic signs. Some of these old people show the characteristic clinical picture described in this study; others present the physical stigmata of old age, but remain more or less oriented and retain their memory for remote events, with pronounced defects in recall of recent occurrences. They often confabulate in an effort to conceal these defects but cooperate to the best of their ability with the hospital routine. They do not show the restless motor activity of the other group, and the histologic changes in their brains are nonspecific. There are also well-known cases of persons in their 9th or 10th decade who remain intellectually alert, or who are even engaged in scientific and professional pursuits, with practically no evidence of cerebral malfunctioning. Since the brains of such presumably normal persons are usually not available for histologic study, one can only surmise that the central nervous system is in a relatively good state of preservation. In the literature in which a few studies have been reported, plaques and neurofibrillary changes are occasionally described, but not in overwhelming numbers. It does not seem logical to assume that argyrophilic plaques and neurofibrillary changes are

18. Wertham, F.: The Brain as an Organ, New York, The Macmillan Company, 1934.

19. Cohn, R.; Raines, G. N.; Mulder, D. W., and Neumann, M. A.: Cerebral Vascular Lesions: Electroencephalographic and Neuropathologic Correlations, Arch. Neurol. & Psychiat. **60**:165, 1948.

20. Critchley, M.: The Nature and Significance of Senile Plaques, J. Neurol. & Psychopath. **10**:124, 1929; Neurology of Old Age (Goulstonian Lecture), Lancet **1**:1119, 1931.

21. Mayer-Gross, W.: Recent Progress in Psychiatry: Arteriosclerotic, Senile and Presenile Psychosis, J. Ment. Sc. **90**:316, 1944.

a normal concomitant of old age, since so many aged patients with psychotic manifestations fail to show these structures, as noted in this study. The etiology of the plaques and nerve-cell changes is outside the province of this presentation, but interesting theories have been suggested by Ferraro,[22] Alexander and Looney,[23] and von Braunmühl.[24] The most likely data indicate that Alzheimer's disease should be classified as a disorder of metabolism, and not as a presenile psychosis. The fact that Pick's and Alzheimer's disease both show changes in nerve cells, demonstrated clearly only with silver-staining techniques, and that both types of change are to be seen in a small percentage of cases, is another factor in classifying the two conditions as disorders of metabolic activity of unknown etiology.

Although certain neuropathologists[25] have tended to discount the importance of plaques and neurofibrillary changes in the etiology of dementias, citing the evidence of their occurrence in "normal" old age, the fact that practically all the patients in our series who showed large numbers of plaques and the characteristic cell changes had a very similar clinical syndrome points to a definite relationship. Furthermore, many old people with a less dramatic mental aberration failed to show these definite histologic alterations.

Since the selection of the limiting parameter of age is probably subjectively determined by the age of the observer, there is no valid reason that the type of "presenile" dementia designated as Alzheimer's disease and certain forms of "senile" dementia with the same clinical manifestations and pathologic changes should be considered as separate entities. It is thus an inescapable conclusion that one should no longer speak of Alzheimer's disease as a presenile dementia. The clinicopathologic picture remains the same regardless of the age of onset. If the classification of Alzheimer's disease is reserved only for those persons who exhibit the clinical signs before the age of 50, how then should one designate the group of patients with exactly similar clinical and pathologic features who do not, however, show the progressive mental deterioration until they have passed the ill-defined barrier between middle age and old age, or who manifest the symptoms in the third or fourth decade? Unquestionably, when the symptoms do develop in the younger age group, especially in persons of high intellectual attainments, the picture is striking enough to warrant perhaps a special category. But at St. Elizabeths Hospital cases of such an early onset are exceedingly rare. On the other hand, cases in which the onset is exhibited in the seventh and eighth decades are numerous.

The work of Alpers, Forster, and Herbut[26] clearly demonstrates that the presence of peripheral and retinal arteriosclerosis is not a diagnostic criterion for the diagnosis of psychosis with cerebral arteriosclerosis. They stated in their summary:

22. Ferraro, A.: Origin and Formation of Senile Plaques, Arch. Neurol. & Psychiat. **25**:1042, 1931.

23. Alexander, L., and Looney, J. M.: Histologic Changes in Senile Dementia and Related Conditions: Studied by Silver Impregnation and Microincineration, Arch. Neurol. & Psychiat. **40**:1075, 1938.

24. von Braunmühl, A.: Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderungen, Ztschr. Neurol. u. Psychiat. **142**:1, 1932.

25. Wertham.[18] Weil, A.: Textbook of Neuropathology, Ed. 2, New York, Grune & Stratton, Inc., 1945. Lichtenstein, B. W.: A Textbook of Neuropathology, Philadelphia, W. B. Saunders Company, 1949.

26. Alpers, B. J.; Forster, F. M., and Herbut, P. A.: Retinal, Cerebral and Systemic Arteriosclerosis: Histopathologic Study, Arch. Neurol. & Psychiat. **60**:440, 1948.

The presence of retinal arteriosclerosis indicates the possibility of cerebral arteriosclerosis, involving the basilar artery, but gives no indication of the state of the arteries and arterioles of the cerebral cortex, meninges and basal ganglia. The absence of retinal arteriosclerosis is not an indication of the absence of cerebral arteriosclerosis, considered in terms either of the group or of any specific vessels studied.

They found, indeed, that retinal arteriosclerosis was relatively infrequent in cases of cerebral arteriosclerosis. The last case discussed in our miscellaneous group is an instance in point. While there was widespread degeneration of the walls of many small cerebral vessels, with concomitant narrowing of the lumen and a few vascular occlusions, most prominent throughout the cortex, there was no clinical evidence of elevation of blood pressure, and no peripheral or retinal arteriosclerosis. Furthermore, the patient manifested no psychotic content but was considered only slightly subnormal mentally. This striking example is strongly suggestive that cerebrovascular disease per se may not be responsible for many of the dementias of late middle and subsequent years.

In rare cases in our series, patients with numerous small cortical infarcts showed a mental picture very similar to that of Pick's or Alzheimer's disease. Since the lesions probably occurred successively rather than simultaneously, there would likewise be a progressive dementia. In the classification of Rhein, Winkleman, and Patton [27] the patients should be in the group they designated as progressive arteriosclerotic psychosis. The data accumulated during this study tend to confirm the pragmatic value of the categorization of arteriosclerotic conditions of these authors.

On the basis of this survey and a previous analysis,[4] it is believed that the two progressive degenerative brain diseases—Pick's and Alzheimer's—should be classified together as disturbances of metabolism, since the clinical conditions are frequently indistinguishable. Air encephalograms may aid in the differential diagnosis, since in lobar sclerosis the atrophy is asymmetrical and in Alzheimer's disease the atrophy is usually diffuse. However, not infrequently a brain which shows elective shrinkage of one temporal lobe (the usual site) may on microscopic study display the characteristic changes of Alzheimer. Furthermore, brains are occasionally seen which present no gross atrophy and yet show histologic changes of this condition. The final verification of the clinical diagnosis can in certain instances only be derived from microscopic evaluation.

The outstanding conclusion is that Alzheimer's disease is a morbid entity that occurs more frequently in the senile age period, but may appear at any earlier time. The earliest age of onset reported in the literature is 16 years.[11] There is no distinguishing characteristic to differentiate the clinicopathological process in the various age groups. The clinical picture is invariable; however, since the disease is not fatal, unless the patient progresses to a vegetative existence, the terminal condition depends on the stage of the pathological process at which death occurs from intercurrent illness. The picture at the time of hospitalization is also variable, since environmental factors influence the period of the disease at which the patient is admitted for custodial care.

SUMMARY AND CONCLUSIONS

Histologic studies by means of silver techniques were carried out on the brains of 210 patients in an attempt to correlate the recorded clinical changes with the

27. Rhein, J. H. W.; Winkleman, N. W., and Patton, C. A.: Mental Conditions in the Aged, Arch. Neurol. & Psychiat. **20**:329, 1928.

pathologic alterations. As a concomitant of the widespread formation of argyrophilic plaques and neurofibrillary changes, a definite clinical picture emerged from the survey. This semeiotic pattern was remarkably consistent regardless of the age of onset of the mental symptoms. It is characterized by slowly progressive intellectual deterioration. Restless wandering, particularly at night, is characteristic; later, when motor activity becomes restricted, there is aimless picking at objects in the immediate environment. Verbal output decreases, and "aphasia" ensues when primary speech and speech associated areas are involved. Other neurologic signs, such as forced grasping and pseudobulbar paralysis, are late concomitants. The clinical picture may appear at any age; there is no relation between the severity of the pathologic process and the age at which mental signs are first manifested.

Argyrophilic plaques and neurofibrillary changes are not characteristic of old age per se.

Since there is no difference in the clinical or pathologic picture in the various age groups, the postulation is made that Alzheimer's disease is a specific entity, and not a "presenile" dementia.

Addendum.—Since the completion of our study on Alzheimer's disease, Dr. Winfred Overholser has called to our attention several early articles on the subject, and has placed at our disposal the *New England Medical Gazette* of September, 1912,[28] in which they appeared. Dr. Solomon C. Fuller, of Westboro State Hospital, Westboro, Mass., not only reported a "classical" case of Alzheimer's disease but made a detailed histologic study of a group of 33 "elderly patients dying insane," 6 old people without psychosis, and a miscellaneous group of 50 younger psychotic persons. (His study was, therefore, very similar to our own.) He also reviewed the available literature, which comprised the reports of some 10 cases of Alzheimer's disease (his was the 10th reported case) and several studies on senility. He concluded that the clinical and pathologic changes in the younger age group designated as suffering from Alzheimer's disease or presenile dementia were similar to those observed in the severest type of senile dementia, and that arteriosclerosis was not the underlying etiologic agent. He noted, too, that the disease in these patients was "not of the sort commonly designated as simple senile dementia." The majority of the early observers, including Alzheimer, commented on the similarities between the presenile patients and certain of the senile group and stated that there was "no good ground for supposing a special pathognomic process" for the younger series.

Of further historical interest is the fact that one of the early cases which Dr. Fuller included in his survey was the subject of a report by Dr. Lafora [29] concerning a patient at St. Elizabeths Hospital, where Dr. Lafora was working at the time. Dr. Lafora stated that his was the fifth recorded instance of Alzheimer's disease.

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28. Fuller, S. C.: A Study of the Miliary Plaques Found in Brains of the Aged, New England M. Gaz. **47**:479, 1912; Alzheimer's Disease (Senium Praecox): Report of a Case and Review of Published Cases, ibid. **47**:635, 1912; also J. Nerv. & Ment. Dis. **39**:440, 1912. Fuller, S. C., and Klopp, H. I.: Further Observations on Alzheimer's Disease, ibid. **47**:669, 1912; also Am. J. Insanity **69**:17, 1912-1913.

29. Lafora, G. R.: Beitrag zur Kenntnis der Alzheimerschen Krankheit oder präsenilen Demenz mit Herdsymptomen, Ztschr. Ges. Neurol. u. Psychiat. **6**:15, 1911.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Harold Voris, M.D., President, in the Chair
Regular Meeting, Jan. 13, 1953

Pick's Disease. Dr. Herman Josephy.

Pick's disease seems to be extremely rare among the patients of the Chicago State Hospital; the case presented by the author is the first encountered in 1,000 autopsies. The patient, a woman aged 59 at the time of her death, exhibited the clinical picture of progressive dementia, without signs of aphasia and apraxia. Therefore, no diagnosis could be made during life. Anatomically, there was symmetrical atrophy of the temporal lobes and of the orbital gyri. Microscopic examination revealed devastation of the cortex. Many swollen nerve cells were present. The author suggests that the term Pick's disease, or Pick's lobar atrophy, should be restricted to cases in which the atrophy is due to a devastation and shrinkage of the cortex. Cases in which the atrophy is caused by other pathological changes should be classified differently.

The grouping together of Alzheimer's disease and Pick's disease as presenile dementia is unjustified and should be abolished. Neither of these two diseases has any relation to true senile dementia, nor are they related to each other. Both should be classified as heredodegenerative diseases of the brain.

DISCUSSION

Dr. Percival Bailey: I was interested in the location of the atrophy and its relation to the mentality of the patient. Since the days of Franz Joseph Gall, we have tended to put the rational faculties in the frontal lobes. We know now from a great deal of evidence produced by the surgeons that many of these patients with atrophy have defects which do not point to the frontal lobes. Of course in a case like this one must make a complete examination of the brain, and in this particular brain the predominant atrophy seems to be posteriorly situated. We know that the posterior association area, including a large part of the temporal lobe, shows a greater proportion of increase in man than does the frontal region. There are many indications that the temporal cortex is the most highly developed. For example, it has few direct connections with the thalamus. I think that in this particular case complete cytological study of the rest of the cortex would be of interest.

Dr. Roland P. Mackay: It is very interesting to me to hear Dr. Josephy point out how rare Pick's disease is in this country, as compared with Alzheimer's disease. It occurs to me that the pathological diagnosis of Pick's disease is much more definite than that of Alzheimer's disease. Pick's disease is one of the lipoidoses, whereas Alzheimer's disease involves the fibrillary structure of the nerve cell. Thus, Pick's disease deviates qualitatively from the normal, whereas there is nothing in Alzheimer's disease that may not be found in any senile brain if the condition progresses far enough.

Does Dr. Josephy think that the apparently greater frequency of Alzheimer's disease may be due to diagnostic confusion with "normal senility"?

Dr. Herman Josephy: One of my main reasons for presenting this paper was to stress the rarity of Pick's disease, at least in this area.

The final diagnosis and differentiation from Alzheimer's disease are made from the findings in the brain. In many instances it is up to the examiner as to whether he will classify a brain with an abundance of plaques and Alzheimer fibrils as one of Alzheimer's disease or one of senile dementia. If the patient became demented in the 4th decade of his life and died in the 5th, the decision is easy; however, if dementia started 10 years later and death occurred in the 60's, the classification is doubtful and to some degree arbitrary.

As to Dr. Bailey's comment, I have a number of sections from the frontal lobe, and the cortex here seems to be well preserved except in the orbital gyri.

Pneumoencephalography, of course, is a great help in establishing the differential diagnosis of Alzheimer's and Pick's disease.

Nystagmus. Dr. C. Wilbur Rucker, Rochester, Minn.

Nystagmus may be classified in a variety of ways. One of the most fruitful employs an anatomic basis, recognizing types of nystagmus that arise through disturbance of vision, stimulation or depression of the labyrinths, weakness of the extraocular muscles, or lesions in the central nervous system. Of the first three types, there are both physiologic and pathologic varieties. Nystagmus due to a lesion in the central nervous system is always pathologic.

Physiologic optic nystagmus may be induced by watching a train of moving targets. As it exhibits quick and slow components, it is called "jerky." Pathologic optic nystagmus results from poor vision and is pendular.

Vestibular nystagmus is jerky, is accompanied by vertigo, and does not change its direction on change of gaze.

Muscular nystagmus consists of intermittent jerks in the field of weakened muscles.

Central nystagmus is jerky, is usually not accompanied by vertigo, and may beat in any direction—horizontal, vertical, or rotary, or in any combination of these. Change of gaze may change its direction. The movements of the two eyes may be dissociated.

A few varieties of nystagmus do not fit into this scheme.

DISCUSSION

Dr. Meyer Perlstein: In cases of spasmus nutans one eye generally exhibits more nystagmus than the other. We have observed that occlusion of the eye with the most pronounced nystagmus decreases the head rolling, while occlusion of the less involved eye increases the head rolling. Would you comment on this observation?

Dr. Roland P. Mackay: Dr. Rucker said that the nystagmus associated with visual defects occurs only in persons born with such defects or acquiring them very early in life. What about miner's nystagmus?

Effects of a Fibrosis-Inhibiting Substance on the Innervation of Muscles by Nerve Implants. Dr. Hyam Hoffman, Melbourne, Australia.

Administration of an antifibrotic, pyrogenic bacterial polysaccharide complex (Piromen) was found to inhibit the formation of neuromas and barrier tissue following implantation of a central nerve stump into muscle in the rat. In place of such tissue, a delicate stroma was formed, rich in reticuloendothelial and Schwann-cell elements. Through this tissue the nerve fibers advanced readily, penetrating intact muscle in large numbers and for substantial distances. Extensive new innervation was achieved, even in already innervated muscles. In denervated muscles, the peripheral stump of the transected nerve was invaded and the entire muscle reinnervated in normal fashion, quite apart from the end-organs formed in the vicinity of the implant. It is concluded that this drug renders the reinnervation of muscles by direct implantation a practicable technique.

DISCUSSION

Dr. Harold C. Voris: In his clinical use of Piromen, does Dr. Hoffman use doses that produce a febrile reaction in the patient?

Dr. William F. Windle: This drug appears to have inhibited the formation of the usual neuroma on the implanted nerve and made possible a richer neurotization of the muscle than was seen in the nontreated specimens. Dr. Hoffman goes into more detail in his manuscript in regard to that point, particularly with respect to certain humoral factors.

Dr. Richard Richter: That is, he would get a richer innervation in the denervated muscle.

Dr. William F. Windle: He got a richer innervation of the denervated muscle, as well as good hyperinnervation of the nondenervated muscle.

In answer to Dr. Vori's question, I can say that the drug is being tried clinically in low febrile doses for disorders of the central nervous system. In order to be sure that it crosses the blood-brain barrier, fever, chills, and other side-reactions may be taken to indicate a reaction on the part of the central nervous system. There is evidence that the drug does not pass the blood-brain barrier with facility. It is effective when given to animals intrathecally in doses one-hundredth to one-five hundredth as great as those producing fever and other reactions by the intravenous route.

QUESTION: How long should one keep up use of the drug?

DR. WILLIAM C. WINDLE: We do not know. Actually, we have little clinical evidence that the drug is of benefit in disorders of the human spinal cord. If the drug was administered to a patient with known transection of the cord immediately after the accident, and if the severed ends of the cord were well approximated, then, judging from the results in animals, one would expect no indication of anatomical regeneration in less than a month and no physiological changes in less than three to four months—perhaps longer.

Experiences with Hypophysectomy in Man. DR. ROLF LUFT and DR. HERBERT OLIVECRONA, Stockholm, Sweden.

Our experience with hypophysectomy in man comprises 27 cases: 3 of Cushing's syndrome, 7 of malignant hypertension, 4 of diabetes mellitus, and 12 of malignant tumors. In Cushing's syndrome coagulation of the pituitary or incomplete removal should be made. So far, malignant hypertension seems not to be suitable for this operation, at least not until some form of premedication or some change in the technique makes it possible to avoid the ensuing acute cerebral edema. The same holds true for diabetes mellitus. The carcinomas of the breast, and possibly also of the prostate, as well as the chorionic epitheliomas in a stage at which other methods of treatment are no longer effective, in our opinion offer a promising field for hypophysectomy. In these cases the operation is comparatively free of danger and is well tolerated.

Harold Voris, M.D., President, in the Chair
Regular Meeting, Feb. 10, 1953

The Ciliospinal Reflex in Injuries of the Cervical Spinal Cord in Man: The Pathway for Pupillary Dilatation in Man. DR. ALEX J. ARIEFF and STANLEY W. PYZIK.

Although there is evidence in the literature that papillary dilatation is by way of parasympathetic inhibition instead of sympathetic excitation, this is applicable to animals like the cat, and has never been proved in man. In monkeys painful stimulation, as in the ciliospinal reflex, causes pupillary dilatation by way of sympathetic pathways. This is also true in man, since in complete lesions of the cervical cord painful stimulation above the lesion fails to cause pupillary dilatation (loss of descending impulses), while stimulation on the chest wall below the lesion results in pupillary dilatation, as well as other sympathetic symptoms, by way of the thoracic sympathetic outflow.

In a review of the lesions of the cervical cord in man, Horner's syndrome was not encountered in chronic lesions above the eighth cervical segment.

Dilatation of the pupil in darkness occurs in man with lesions of the cervical cord and is most likely not the result of sympathetic stimulation by way of the ciliospinal center (inability of suprasegmental impulses to descend), but probably is due to a reversal of the light reflex.

DISCUSSION

DR. WALTER FREEMAN, Washington, D. C.: It is known that when an organ is removed from direct innervation it becomes more sensitive to epinephrine. I should like to ask the authors whether they have any suspicion that a generalized stimulation is produced, the stimulation of epinephrine production. Perhaps psychic stimulation would enter into the production of pupillary dilatation.

DR. ALEX ARIEFF: Dr. Lichtenstein is responsible in part for this presentation. Some years ago, when I got into paraplegic work at the Veterans Administration Hospital at Hines, he asked me whether I ever saw Horner's syndrome in patients with lesions of the cervical cord. I became

interested and examined the patients with this in mind. I never saw a complete Horner syndrome. I saw inequality of pupils and palpebral fissures, but never the complete syndrome. Dr. Pollock suggested that I test for the ciliospinal reflex in cases of lesions of the cervical cord. The ciliospinal reflex is actually what the literature suggests. It is the result of a painful stimulus that has its optimal point of stimulation on the face. Dr. Lichtenstein's theory that the sympathetic fibers branch out from the internal carotid artery to the vertebral artery may well be true. In the Wallenberg syndrome it is possible that some sympathetic fibers are destroyed, and that that is the reason for the Horner syndrome, rather than the neurologic lesion per se. It would be helpful to get an ophthalmologist interested in these patients.

In reply to Dr. Freeman's first question, it is true that a denervated organ is more sensitive to stimuli. We showed this, and Foerster mentioned it. I have not tried out the effect of epinephrine or cocaine on the pupillary reaction. The pupillary response with painful stimuli was a crossed one; i. e., the contralateral pupil dilated more than the ipsilateral one. I doubt whether this response is due to epinephrine sensitivity; if it were, it would also occur with painful stimuli to the face, and this did not occur in lesions of the cervical cord.

In answer to his second question, by psychic stimuli we mean that while we were making preparations for the testing we could see a dilatation of the pupil and inferred that psychic stimulation was going on. The pupil would contract and then dilate. I made a note that it fluctuated.

Hazards of Lobotomy: Report on 2,000 Operations. Dr. Walter Freeman, Washington, D. C.

A comparison of the Freeman-Watts series of prefrontal lobotomies (624 patients; 702 operations) and the series of transorbital lobotomies (1,234 patients; 1,303 operations) shows that the operative fatality was about twice as great in the former, i. e., 3.4% versus 1.6%. Most of the deaths following transorbital lobotomy have been due to hemorrhage; the other fatal complications have been rare. As postoperative complications and sequels, prefrontal lobotomy has had a much higher incidence of the "frontal lobe syndrome," obesity, and convulsive seizures. When patients who had convulsions prior to operation were excluded, the figures were close to 20% for prefrontal lobotomy and 1% for transorbital lobotomy. The final hazard is the danger of delay, since good results in terms of social rehabilitation were 65% in patients operated upon after less than six months of hospitalization, 50% in patients hospitalized a year, and 35% in patients hospitalized two years. Improvement may still occur in patients hospitalized for more than 10 years but seldom is sufficient to restore them to working capacity. The operations are about equally effective in restoring patients to useful life. Prefrontal lobotomy has been practically abandoned in favor of transorbital lobotomy.

DISCUSSION

Dr. Percival Bailey: Dr. Freeman has paid me the honor of asking me to open the discussion. I was present when he visited the Society and talked about lobotomy for the first time. I was then hesitant about accepting it; but, being entirely ignorant of the matter and without personal experience, I was willing to maintain an attitude of reserved judgment. I have at present little more experience than I then had. However, I have read about the experience of a great many other people and have thought much about the matter. We know that lobotomy is not the ultimate answer to the handling of psychiatric patients, and that it cannot be the answer to the troubles of thousands of people in our state hospitals. But all other methods which have been proposed are merely palliative in most cases. If, by the method of lobotomy permanent results can be obtained without too great disability or too great risk, nobody has the right to reject the treatment on the basis that it is a mutilating operation. We take out part of the thyroid gland or part of the kidney if the patient is going to benefit thereby. There is no reason that we should not take out part of the brain, unless we fall back on the metaphysical objection that we thereby take out part of the soul. Accepting, therefore, the position that the method is justifiable under certain conditions, and that we will guard against its abuse as we do in cases of other operations, we may discuss how the operation is to be done.

Dr. Freeman prefers a transorbital method, perhaps because he is not a surgeon. Surgeons are reluctant to adopt this method because it violates one of the fundamental principles of surgery, that the surgeon must see what he is doing. The surgeon is very certain to obtain adequate exposure so that he may avoid complications. This is not necessarily a contraindication to the

transorbital procedure. Many nonsurgical interventions are made on the human body every day. A transorbital lobotomy can perhaps be justified if it is performed in a hospital where surgical help is available if complications arise, as they apparently do. I cannot, however, see how it is possible to justify doing the operation in an office where surgical aid is not available. Furthermore, I do not personally see how there is any advantage over the open method.

Dr. Freeman has presented us with statistics, but we all know that statistics must be interpreted. In his present statistics he has included a great many surgical lobotomies which were done early, when he lacked experience, and which furthermore, were far more radical than a transorbital lobotomy. It is possible, by the open method, to make equally restricted incisions in the frontal lobe, and I personally shall not be too much impressed until we have figures based upon such interventions. I am also not convinced that such a limited procedure made by the open method would lead to any greater amount of psychological difficulty than a transorbital lobotomy.

I was rather surprised to see the direction of the incision made in a transorbital lobotomy. It seems to me that the cut extends anteroposteriorly in a direction not calculated to sever the connections with the prefrontal cortex. This is probably due to the fact that the leucotome cannot be moved very far except in the anteroposterior plane and therefore largely pushes the brain aside, except in the anteroposterior direction. I am sure that Dr. Freeman did not mean to say that there are no blood vessels in the area sectioned by his leucotome. He probably meant to say that there are no large arteries or veins, the sectioning of which would give rise to a disastrous hemorrhage.

In short, there seems to me to be sufficient evidence accumulated at the present to justify frontal lobotomy in certain cases because the patient gains from the intervention in certain ways and these gains are greater than the losses produced by the disturbance of the functioning of the frontal lobes. The method of producing the incision is still debated, but it seems to me that the indications and contraindications are beginning to be generally understood.

Dr. Wendell J. S. Krieg: I was interested in Dr. Freeman's reference to the thalamic radiation to the frontal lobe. The first lantern slide showed quite clearly the forward passage of the thalamic radiation from the anterior limb of the internal capsule, and here it must be if it is going to the prefrontal region. In the second picture, that of a horizontal section of an approximately one-month-old infarct, in which the intracerebral tracts were just becoming myelinated, was indicated the tract as it comes through the anterior limb and then passes medially. At the time Flechsig did his work he was not in the position to say what the thalamic connections of the frontal lobes were. It is only recently that we have found they are from the medial nucleus. R. A. Pfeiffer, who made beautiful three-dimensional reconstructions, indicates this as one of the four myelinated tracts in the cerebrum. He calls it a different name, but it is apparently the radiation from the anterior nucleus of the thalamus, as in other animals, to the cingulate cortex.

In the prefrontal lobotomy in the monkey, the thalamic radiation lies more nearly just under the gyri as they reach the anterior parts. The more central region is given over to descending fibers. Considering how medially Dr. Freeman's lobotomy lesion passes, one obtains the impression that he is cutting the radiation of the anterior nucleus to the cingulate cortex, which has recently been shown to be related to the personality and emotional life of the individual. In this case the operation might be more effective by section of the nucleus by a stereotaxic machine. If man is anything like the monkey, I do not think that radiation of the medial nucleus is being cut, since this must go to Areas 9, 10, 11, 12, and 44, some of which are far lateral.

Dr. Milton Tinsley: It is a little presumptuous for us to talk about lobotomy in view of the number of Dr. Freeman's cases. At the state hospital with which I am associated we have been doing all lobotomies by the open Lyerly method. We have never used the closed lobotomy or the transorbital method. We have tried various types of procedures, in patients who have very severe psychiatric disorders; we do not get any patients with minor disturbances or with illnesses of short duration. We tried topectomy and bilateral medial lobotomy. The psychiatrists have been very unhappy with the results of topectomy or medial lobotomy. They are happy with the results of the radical bilateral prefrontal lobotomy. I should like to know how the transorbital and the prefrontal lobotomy compare in the cases of severe disease, and whether the prefrontal or transorbital lobotomy gives better results in those cases.

DR. PERCIVAL BAILEY: May I ask Dr. Tinsley whether he did or did not remove the gyrus cinguli?

DR. MILTON TINSLEY: I did not.

DR. HAROLD C. VORIS: I had the privilege of reading Dr. Freeman's paper beforehand. It seems to me that one of the very valuable things in this presentation is the discussion of the complications, both surgical and nonsurgical, in this large group of patients, particularly in the group with prefrontal lobotomies who have been observed over such a long period. Those figures are certainly worth while from the standpoint of telling us what chances these patients have of undesirable sequelae, such as the frontal lobe syndrome, marked obesity, and, particularly, convulsions. The value of that part of the paper should be emphasized.

As Dr. Bailey said, surgeons are not apt to be fully satisfied with procedures which are carried out blindly unless they are certain that they can be well controlled. My own experience with transorbital lobotomy is limited to a very small group of patients in whom the procedure was carried out for intractable pain. Postmortem examination in the one fatal case in this group revealed a marked asymmetry in the point where the instrument had entered the orbital plate, as well as in the section in the frontal lobe. The fatality was due to hemorrhage on the side where the section of the frontal lobe was badly placed. I felt after that that I could not adequately control the section with the transorbital method and so have not done the operation in any more cases. That, of course, is a confession of technical failure. All of us know that additional practice with procedures of this type does lead to increasing proficiency of the method, as witness the increased proficiency with puncture of the carotid artery at the site of the common carotid artery.

The criticism that prefrontal lobotomy is more likely than transorbital lobotomy to produce undesirable or serious sequelae can in part be obviated by lessening the radical nature of the operation. I believe that in Dr. Freeman's series of prefrontal lobotomies only an inferior quadrantic cut was made in some cases. I wonder if he has any figures on whether or not lessening the extent of the prefrontal operation decreases the complications, which admittedly are greater in the prefrontal lobotomies.

DR. ROLAND P. MACKAY: I infer from Dr. Freeman's figures that the disagreeable aspects of transorbital lobotomy are less than those of the orthodox operation. That might be correlated with the fact, which he shows, that it involves resection of much less brain tissue. Work in recent years has shown that changes in personality after frontal lobotomy are proportional to the amount of tissue destroyed. Dr. Freeman himself has previously shown that therapeutic results and undesirable disturbances in behavior are to be expected from frontal lobotomy in proportion to the posterior location of the section made. Thus, transorbital lobotomy would appear to involve less hazard, but also to promise less beneficial results, than the orthodox lobotomy.

It is perhaps beyond the scope of Dr. Freeman's discussion to describe the end-results of his transorbital lobotomy, but I should like to ask him whether the operation is adequate in many cases in which the more standardized procedure is applicable.

DR. WALTER R. KIRSCHBAUM: Did Dr. Freeman also observe serious metabolic disturbances leading to marantic states and death from uremia about two to six months after frontal lobotomy, as English authors (McLardy) have reported? In this group of fatal cases examination showed excessive destruction, reaching into the cingular gyrus and other supposed-to-be-higher autonomic centers.

DR. WALTER FREEMAN, Washington, D. C.: There are two questions: First, is it safe? Second, is it effective? An incomplete operation is useless; an effective operation is worth while. From the beginning it has been noted that in lobotomy one-third of the patients get well, one-third improve, and one-third do not improve. Only this past week I checked the patients in West Virginia, where I had operated on 232 in the summer of 1952. At the end of six months 83 were out of the hospital, 72 were improved, and 72 were unimproved. There were four operative deaths and one later death. Apparently, transorbital lobotomy was as effective as prefrontal lobotomy. I will agree that the fibers in the lower part of the frontal lobe seem to be somewhat more important than those in the upper part, for on a number of occasions on which the first lobotomy has failed (and this applies to both the prefrontal and

the transorbital) secondary operations with section of deeper fibers, and separating the frontal lobes more completely from the thalamus, have sometimes succeeded. The chances of success with secondary lobotomies are about 50-50. Once in a while, as Dr. Kirschbaum suggests, there are disturbances of metabolism, uremia, and trophic disturbances, and they occur usually when the incisions go too far back. I have seen a few such sequelae in the prefrontal series when we were doing an extremely radical lobotomy as far as 2.5 cm. behind the coronal sutures and impinging upon Areas 6 and 8. I do not recall ever seeing such an occurrence after transorbital lobotomy.

There are definitely fewer personality alterations in the more restricted operations, but there is the risk of the patient's relapsing. Just the other day a man brought in his daughter, saying she "was wonderful" for four and one-half years; then her mother died, and she relapsed and was hearing voices again. Relapses can occur 5 and even 10 years after lobotomy. At the same time some patients take a long time to improve, even after the transorbital operation. Some patients may take two years to get out of the hospital and five years to find a way of life.

The incisions of transorbital lobotomy sever the thalamofrontal radiation as it passes between the insula and caudate nucleus and the anterior horn of the ventricle. To reach the base, the fibers extend out over the anterior commissure. Beyond the frontal horn there is a bend, or elbow, in the radiation, which one can see pretty well in a four to seven months' infant. I do not think that it is the radiation from the anterior nucleus that is severed in these transorbital operations, because examination of the thalamus shows degeneration only in the medial nucleus. It was only in the prefrontal series that we found involvement of the cingulum and corresponding degeneration of the anterior thalamic nucleus.

Dr. Voris spoke about asymmetrical incisions in transorbital lobotomy. That brings up the question of the skill which is necessary in performing the operation. I would recommend that anyone who undertakes it practice on the cadaver until he gets the feel of it. Descriptions in the literature do not mean very much until you are right in there. In order to preserve the symmetry, it is preferable to introduce both instruments successively and then stand behind the patient's head and manipulate the instruments so that they will always be maintained at a certain angle with the sagittal plane.

I wonder whether Dr. Bailey had a chance to look at the specimens. It looks at first as though the deep sagittal section was in the direction of the thalamofrontal radiation rather than across it. But the radiation from the thalamus has to be regarded in three dimensions, many fibers curving medially anterior to the ventricle. The Z-shaped incision severs the radiation. When this procedure is done with local anesthesia in cooperative patients, one gets startling elimination of distress, anxiety, and fear of pain. Some patients even get off the table as though nothing had happened to them.

Dr. Bailey has mentioned the moral and ethical aspects of lobotomy. This will be the subject of discussion at the meeting of the American Psychiatric Association in Los Angeles in May. I agree with him that a part of a patient may be sacrificed for the benefit of the whole. Two assumptions must be made: first, that the patient will not get well without such intervention, and, second, that the results cannot be achieved in any other manner. We have in our country many patients who are disabled, patients who are suffering, patients who have been treated by various methods ineffectively; and with the above qualifications I think we are justified in proceeding with transorbital lobotomy. I do not think that, in the face of these hazards, we are justified in recommending prefrontal lobotomy, with a 25% convulsion rate, a 22% obesity rate, a 3.5% death rate, and a 10% incidence of the frontal lobe syndrome. These are too high to justify the use of prefrontal lobotomy. When I came here some five years ago I was quite enthusiastic about prefrontal lobotomy. During the past two years we have practically abandoned prefrontal lobotomy in favor of transorbital lobotomy.

Octamethyl Pyrophosphoramide in Treatment of Myasthenia Gravis: Further Observations. Dr. Sidney Schulman, Dr. J. Alfred Rider, and Dr. Richard B. Richter.

Octamethyl pyrophosphoramide is the most recent of the organic phosphorus anticholinesterase agents to be used in the treatment of myasthenia gravis. Like the other organic phos-

phorus compounds, such as diisopropylfluorophosphate and tetraethylpyrophosphate, and in contrast to neostigmine, octamethyl pyrophosphoramide inhibits cholinesterase irreversibly, and so has the advantage over neostigmine of a longer duration of action. Its advantages over the other phosphorus compounds lie in its greater chemical stability and less severe toxic side-effects.

The results of the treatment of the first six patients with octamethyl pyrophosphoramide were reported by our group early in 1951 (*J. A. M. A.* **145**:967, 1951). Since then, two more reports, by other investigators, have appeared (Wilson, C. W.; Williams, J. P., and Miller, D. H.: *Ann. Int. Med.* **37**: 574, 1952. Gregory, L.; Futch, E. D., and Stone, C. T.: *Am. J. Med.* **13**:423, 1952), and both these groups have concluded that octamethyl pyrophosphoramide is the most satisfactory drug now available in the management of myasthenia gravis. Our own experience with the drug at the time of our initial report, two years ago, led us to conclusions that were not quite as sanguine, and with further experience we are even more convinced that octamethyl pyrophosphoramide cannot be endorsed as a substitute for neostigmine without strong reservations.

Our experience with this drug to date consists in its use in 15 patients; 7 of this group have died while under treatment with octamethyl pyrophosphoramide, and two were unable to tolerate the drug because of the development of severe parasympathetic symptoms during the process of substituting it for neostigmine. Of the seven deaths, we believe that three were a result of the drug taken in excessively large doses. These three patients had severe myasthenia. Each was taking more than 50 mg. of octamethyl pyrophosphoramide daily, and in each patient parasympathetic symptoms were minimal and easily controlled by small doses of atropine. In one of them we know that death resulted from sudden and complete respiratory paralysis, which developed about an hour after parenteral administration of 0.5 mg. of neostigmine methylsulfate, in the absence of signs of parasympathetic stimulation, and we have reason to believe that the other two patients died in the same way. The remaining four deaths occurred in patients with severe myasthenia who were receiving small doses of octamethyl pyrophosphoramide and cannot be attributed to the drug.

Six patients in this series have been taking octamethyl pyrophosphoramide for from seven months to two and one-half years, three of them for more than two years. Although four of these patients have mild myasthenia gravis and the disease in two can be classified as of only moderate severity, all of them have been much less disabled on treatment with this drug than when they were taking neostigmine, and all of them are leading active and useful lives. The average dose of octamethyl pyrophosphoramide for these patients is 20 mg. daily. The largest dose is 14 mg. twice a day.

Since the results in patients with mild or moderately severe myasthenia are excellent, we do not mean to discredit the drug completely. We do wish to emphasize, however, that the large doses required by patients with severe myasthenia are close to the upper limit of safety and that death may occur suddenly as a result of an increase in weakness from an overdose, without any warning in the form of an increase in parasympathetic symptoms. For this reason it seems to us impossible to endorse the routine use of octamethyl pyrophosphoramide in the treatment of myasthenia gravis without some rather strict qualifications. We believe that it should not be used in patients with severe myasthenia gravis or, on the other hand, in patients with mild myasthenia who do well on neostigmine. We think there should be a certain maximum dose that should never be exceeded, and we have chosen, somewhat arbitrarily, 30 mg. daily as this upper limit. Finally, the drug should never be given to patients who are uncooperative and who cannot or will not submit to rigid supervision.

DISCUSSION

DR. RICHARD B. RICHTER: Of our seven patients with fatal outcome, we think we have good reason to believe that four died in myasthenic crisis and three from direct intoxication by the drug. The point we wish to emphasize is the stealthy and unheralded way in which this toxicity builds up to its final, sudden catastrophic collapse. We had expected when we began treating patients with octamethyl pyrophosphoramide that toxic symptoms from the muscarine-like action of acetylcholine would give us ample warning of danger. But this has not been so with our patients; in general, they have shown no increased salivation, lacrima-

tion, or gastrointestinal symptoms. It may be that this is accounted for by their taking atropine as a regular part of their treatment. If so, this offers no practical solution to the problem, because, for comfort's sake alone, it has been necessary for almost all of our patients to use atropine if octamethyl pyrophosphoramide is to be given at all.

With increasing weakness, then, as the only indicator of serious toxicity, one can say that it is always difficult, and sometimes impossible, to distinguish between the dose which is insufficient and that which is gravely toxic for a particular patient. It would appear that this margin may be a very narrow one indeed.

While all this sounds very pessimistic, we do not mean to leave the impression that octamethyl pyrophosphoramide has no place in the treatment of myasthenia gravis and that its use should be abandoned. I should like to give somewhat more emphasis to the six successfully treated patients than Dr. Schulman was able to do. For these patients, all of whom had previously been under management with neostigmine, we can say unreservedly that octamethyl pyrophosphoramide has been more satisfactory.

One of them, a woman who was accustomed to a very active social life and much traveling, was restive and discontented because she was so much hampered in her activities while on neostigmine therapy. With octamethyl pyrophosphoramide, which she has taken for two and one-half years, she has been able to resume her former activities fully. The maintenance dose of the drug has never been greater than 18 mg. a day. Last summer she ran her country house full of guests without servants and took long expeditions every day on a dosage of 4 mg.

Another woman, whose disease has been somewhat more than mild, has now been taking the drug, with satisfactory results, for more than two years and is apparently stabilized on a dose of 28 mg. a day. During the period of her treatment she weathered a total hysterectomy and recently had the complete care of two active grandchildren during her daughter's lying-in and her husband's hospitalization for acute coronary thrombosis.

A man with comparatively mild myasthenia gravis had been under treatment with neostigmine for five years. While his improvement was objectively satisfactory, he was, nevertheless, greatly dissatisfied with it and made his own life and that of his family miserable by his consequent bad humor. For that reason he was placed on octamethyl pyrophosphoramide therapy, which was found to give him maximum benefit in a dose of 28 mg. a day. He has been on this regimen for more than two years, has been fairly contented, and works regularly at his job with the city fire department. He was recently commended in the newspapers for his conduct in line of duty.

Since we believe that octamethyl pyrophosphoramide does have a place in the treatment of some myasthenic patients, in spite of the hazards involved, I wish to elaborate a little more on what Dr. Schulman said about the indications for its use. It should certainly be restricted to the treatment of patients with mild, or at the most comparatively mild, symptoms for whom neostigmine in one way or another is not satisfactory and who are intelligent, cooperative, and in a position to be watched carefully. It will sometimes happen that such a patient does well on small doses of the drug for a time, only to have his requirement increase later, just as with neostigmine, with repeated but temporary improvement after each increment in the dose. Under these conditions we would now abandon the use of octamethyl pyrophosphoramide altogether and revert to the use of neostigmine alone, regardless of how unsatisfactory its effects might be.

One of our fatal cases illustrates several of these points. The patient was a young, energetic man living in the backwoods of northern Wisconsin, far from immediate medical attention. We had had him under treatment with neostigmine for a number of years, but with time his neostigmine requirement increased, until he was greatly handicapped by severe general and bulbar weakness, even on large doses. Because of the severity of his symptoms and his inaccessibility, we were reluctant to place him on octamethyl pyrophosphoramide therapy, but finally decided to do so because of his repeated threats of suicide, which we regarded as serious. For many months he did very well, was able to enter again into the activities of his circle of friends, and drove a truck for a living. His case was included among the more favorable ones in our first report. Then, again, his requirement for octamethyl pyrophosphoramide increased; improvement of his symptoms followed as we increased the dosage cautiously, with due warning to him and his local physician to be on the alert for toxic symptoms. We had reason to

believe, however, that, with the heedlessness of youth, he was regulating the dose more or less to suit himself. Then one day, unexpectedly, he was found dying, and he expired within a few minutes after the arrival of his physician.

I believe, too, that some safe upper limit of the dose should be set and never exceeded under any circumstances. Our three patients who died of intoxication were on prescribed doses of 40, 50, and 56 mg. a day, respectively, at the time of the fatal outcome. Patients, however, have died while receiving doses as low as 22 mg. a day. Among those who are doing well, one takes as little as 9 mg. a day, and the largest dose is 28 mg. On the basis of our experience and that reported by others, we have rather arbitrarily set 30 mg. as the upper permissible limit, but with the aim to keep it as much lower than this as possible, consistent with reasonably good therapeutic effect.

DR. SYDNEY SCHULMAN: Two of our patients have taken ephedrine with octamethyl pyrophosphoramide. It seems to have the same potentiating effect when used with this drug as it has with neostigmine. We have not tried Trasentine (a brand of adiphenine) as a substitute for atropine. Generally, patients on a maintenance dose of octamethyl pyrophosphoramide who do not take neostigmine in addition require only small doses of atropine to control the muscarinic side-effects completely. Indeed, in some patients atropine is all too effective in controlling these symptoms, thereby masking the warning signals of approaching toxicity. On the other hand, in patients with severer myasthenia, who still require neostigmine even with moderately high doses of octamethyl pyrophosphoramide, atropine is not as effective, and perhaps for such patients Trasentine would prove useful. But then, again, a deceptively safe situation might result and lead to the temptation to increase the dose of antiesterase drugs to dangerously high levels.

PHILADELPHIA NEUROLOGICAL SOCIETY

Alexander Silverstein, M.D., Presiding
Regular Meeting, Feb. 6, 1953

Report on Cases of Poliomyelitis in Philadelphia in 1952. DR. A. TORNAY, DR. CHARLES LABOCCETTA (by invitation), and DR. ALEXANDER SILVERSTEIN.

During 1952 there were 182 cases of poliomyelitis reported to the Department of Public Health in Philadelphia. In this group there were 16 deaths. Of these cases, 174 were from the Philadelphia General Hospital, Northern Division.

The authors discussed the week-by-week incidence of poliomyelitis, the varieties, and the mortality statistics of the various varieties. They indicated the number of respirator and tracheotomy patients. They also discussed 65 cases in which they revised the diagnosis from poliomyelitis to some other condition. They pointed out that the death rate for 1952 was 9%, whereas for the previous nine years it had been only 3%. It was also pointed out that the incidence of poliomyelitis was higher this year than usual.

The treatment of poliomyelitis was briefly considered.

DISCUSSION

DR. JOSEPH YASHKIN: Were any virus studies done?

DR. CHARLES LABOCCETTA: All patients with the nonparalytic type were studied. No poliomyelitis virus studies were done, as very few laboratories are set up for it, but routine virus studies were made.

DR. JOSEPH YASHKIN: Were any of the agglutination tests positive?

DR. CHARLES LABOCCETTA: One was positive for mumps and one for Leptospira infection.

DR. ROBERT GROFF: What criteria were used for the diagnosis in the nonparalytic cases?

DR. CHARLES LABOCCETTA: The diagnosis was made mainly by exclusion and the spinal fluid studies. The patients must be examined from time to time, and one cannot make the diagnosis on one examination.

Biological Course of Spontaneous Subarachnoid Hemorrhage. Dr. Georges Allégre (by invitation) and Dr. A. Earl Walker, Baltimore.

In this report the biological course was analyzed in 313 cases of proved spontaneous subarachnoid hemorrhage observed during the past 25 years at the Johns Hopkins Hospital. Bleeding secondary to trauma, birth injuries, tumors, and intracerebral hemorrhage in patients over 50 years of age were excluded.

Of the subarachnoid hemorrhages, 126 were due to arterial aneurysms, and 16, to vascular anomalies, and 171 were of unknown origin. The ages of the patients ranged from 5 to 70 years, over 50% of the hemorrhages occurring in those between the ages of 30 and 50.

Of the patients, 40.2% died in the initial attack. Of those surviving, 36.3% died in the second attack. Of the remainder, 28.1% died in the third or a subsequent attack.

The mortality was greatest in the first week following hemorrhage, 35.4% dying in this period. No significant variation in mortality rate was noted between those of known and those of unknown etiology.

The incidence of arterial hypertension was nearly 50%. The mortality of hypertensive patients was 40% the first day, as compared with 10.7% for nonhypertensive patients. After the first week the spontaneous mortality (all cases) was approximately 50% for patients without surgical treatment and 30% for patients with surgical procedures.

Surgical intervention in comatose patients (16) carried an extremely high mortality; all patients having intracranial surgery (5) died. Of all patients having carotid ligation, 9 died. Of 42 noncomatose patients, 13 died; 15 of these had carotid ligation, and 27 had intracranial procedures. At the time of the report, the survivors had been followed from 3 months to more than 10 years; 4 were disabled, and 3 had died of other conditions.

Of the 16 patients with vascular anomalies, 13 were operated upon, with 4 deaths; 3 were well more than five years later; 3 were disabled, and the outcome for 3 was unknown.

DISCUSSION

Dr. Helena Riggs: A review of our cases of ruptured aneurysm, of which there were 143, showed that two-thirds had a history, or autopsy showed evidence, of a previous leak. It was also found that the second hemorrhage occurred within two or three weeks in two-thirds of the cases. I am not sure what the authors meant by hypertension. In all our cases there was elevation of the blood pressure, which was probably cerebral in origin, although there was also heart disease in a large percentage. In only a few cases was operation performed. In three cases cure was spontaneous, in that the patients recovered, and died of another illness.

Dr. Michael Scott: I was interested in the cases of spontaneous intracerebral hematoma and the surgical management in cases of acute apoplexy with signs of a space-taking clot. Of interest in this regard is the case of a woman aged 36 who had had repeated leaks, at approximately yearly intervals, with convulsions, for the past 12 years. An arteriogram revealed a large vascular anomaly, which I should not operate on at present.

Dr. Robert Groff: In the early days our chief thought was of diagnosis, and now we are thinking of treatment. I am interested in the statement that aneurysms are better treated with a delay of a week or so. That is my feeling also. My colleagues and I have done intracranial trapping in 36 cases. In five of these the patient is dead; in six or eight hemiparesis occurred, and in six convulsions developed. The direct surgical approach is the treatment of choice. In my experience, aneurysms of the middle cerebral artery are particularly difficult and I should like to hear the authors comment on this.

Dr. G. A. Gammon: Did the authors see any cases of aneurysm with coarctation of the aorta?

Dr. Georges Allégre: We said the patient had hypertension when he had a history of hypertension for years. The incidence of spontaneous intracerebral hematoma was 1:4, and it was especially high in arteriovenous malformations or angiomas. Five cases of aneurysms with coarctation were seen: Two were asymptomatic, and three had bleeding.

Influence of Aging, Arteriosclerosis, and Hypertension upon the Cerebral Vessels and Their Reactivity. Dr. H. A. Shenkin and Dr. Paul Novack (by invitation).

The cerebral circulations of persons of various age groups and of patients who manifested various degrees of arteriosclerosis and hypertension were studied by means of the nitrous-oxide technique. It appears that aging, arteriosclerosis unaccompanied by hypertension, and hypertension unaccompanied by arteriosclerosis do not significantly alter the cerebral blood flow or the cerebral metabolism. When hypertension and arteriosclerosis occurred together, a marked reduction in cerebral blood flow and cerebral oxygen consumption resulted. The association of hypertension and arteriosclerosis was considered to signify the presence of a much severer and more diffuse degree of arteriosclerosis, particularly of the arteriolar type, than that present when arteriosclerosis occurs without hypertension. The degree of impairment of cerebral blood flow and of oxygen utilization was no severer in hypertensive, arteriosclerotic patients with clinical cerebrovascular disease (history of cerebrovascular accident or mental deterioration) than in hypertensive arteriosclerotic patients with no clinical cerebrovascular disease. It is suggested that the reduced cerebral oxygen utilization noted in hypertensive arteriosclerotic patients reflects impaired ability of the brain to extract increased amounts of oxygen from the blood in response to a decreased cerebral blood flow. It is further hypothesized that the brain cell adapts to the reduction in available oxygen which develops over a period of years by a reduction in its oxygen needs. In an effort to assess the degree to which organic narrowing and functional spasm participate in the increased cerebrovascular resistance noted in patients with these various altered vascular states, the effects of carbon-dioxide inhalations were studied. From these data emerged a clarification of the interrelated effects of hypertension and arteriosclerosis upon the cerebral hemodynamics. In hypertension uncomplicated by clinically evident arteriosclerosis, the cerebrovascular resistance is increased, mostly owing to vasospasm, but in part as a result of arteriosclerosis. This increase in cerebrovascular resistance parallels the increase in blood pressure, and there is no reduction in cerebral blood flow. In arteriosclerosis without hypertension, a normal cerebral blood flow and cerebrovascular resistance are maintained either because the normal vascular tone is relaxed or the arteriosclerotic process is not sufficiently diffuse to involve arterioles. Finally, when hypertension and arteriosclerosis obviously coexist, the arteriosclerosis is of much greater severity and diffuseness than is noted in the absence of hypertension, and the relaxation of vascular tone perhaps noted with arteriosclerosis does not occur; the net effects is a great increase in cerebrovascular resistance with a pronounced reduction in cerebral blood flow and oxygen consumption.

DISCUSSION

Dr. Manuel Sall: Was this test tried on anyone on whom a ganglionectomy had been done?

Dr. Joseph Yashkin: What were the criteria for the diagnosis of arteriosclerosis? I believe that one should not hurry to apply these findings to such problems as senile dementias without further study.

Dr. Helena Riggs: I have the same question about the criteria for the diagnosis of arteriosclerosis. I have seen many brains of patients with arteriosclerotic insanity with no arteriosclerosis of the aorta. If there was no dilatation with carbon dioxide, it would be the first time I know of in which the capillaries of the brain became arteriosclerotic.

Dr. Gabriel Schwarz: Why was the resistance increased after carbon dioxide inhalation in one case?

Dr. Kennedy: We have 20 records of cerebral circulation in children. Most of them were normal. In the age group of 5 to 14 years the oxygen uptake was higher than normal, and the blood flow was also about twice the normal.

Dr. H. A. Shenkin: I did not say that there was evidence of cerebral circulatory changes in senile dementia. As to the criteria for arteriosclerosis, these were chiefly clinical, such as cerebral thrombosis and mental changes. As for Dr. Riggs's question, the results speak for themselves. All of these cases fell in a certain range; some patients died of cerebral changes; some had a calcified aorta.

DR. JOSEPH YASHKIN: If one speaks of arteriosclerosis, one must have scientific data to establish the diagnosis. Is it on the basis of anatomy, age, or clinical evidence?

DR. H. A. SHENKIN: Clinical.

Effect of Corticotropin on Paralysis of Experimental Allergic Encephalomyelitis.

DR. G. A. GAMMON and DR. M. J. DILWORTH (by invitation).

Allergic encephalomyelitis has been produced in the guinea pig by the injection of homologous brain prepared according to the Freund adjuvant technique, with the use of killed tubercle bacilli and liquid petrolatum. Of 189 guinea pigs given injections of the antigen, 113 exhibited unequivocal signs of paralytic encephalomyelitis within 3 to 27 weeks. Fifty-one guinea pigs with unilateral paralysis of the hindlimb were treated with massive doses of corticotropin, 5 mg. intramuscularly every sixth hour for 5 to 21 days. Treatment was begun within 24 hours after the onset of paralysis and was continued for 48 hours after recovery from paralysis or until the condition of the animal had remained stationary for 48 hours. Of this group, 35 animals showed complete symptomatic recovery, 5 showed incomplete recovery, and 8 died during the course of treatment. During the first 24 hours of treatment generalized improvement occurred, manifested by improved appetite and increased alertness and activity; progression of paralysis ceased and a gradual restoration of function occurred between the 3d and the 5th day, becoming complete by the 7th to the 12th day. Re-treatment following relapse on cessation of therapy with corticotropin was uniformly less successful. The guinea pigs which showed a vestibular disturbance unassociated with paralysis exhibited the most rapid response to corticotropin, whereas the animals which had convulsive seizures either initially or during relapse all failed to respond to corticotropin and died. The 50 paralyzed guinea pigs which were not treated all died of progressive ascending paralysis, although five of this group had shown a temporary remission.

None of the animals of the control series showed any histologic evidence of encephalomyelitis. All the animals which died of encephalomyelitis in both the untreated and the treated series showed encephalomyelitic lesions. Animals killed during the course of treatment and those killed at the termination of a successful course of treatment showed minimal evidence of encephalomyelitis. Retention of dye (trypan blue) within the vessels approached that of normal controls within 72 hours of treatment, suggesting that a vascular response underlies the mechanism whereby corticotropin mediates its beneficial effect in allergic encephalomyelitis in the guinea pig.

DISCUSSION

DR. CHARLES RUPP: Were any other histopathological changes found? Were the round-cell infiltrations present in the corticotropin-treated animals?

DR. M. J. DILWORTH: We did not have quantitative studies, but one could tell the difference between sections from untreated and those from treated animals.

DR. MICHAEL SCOTT: Should not this condition be called an encephalomyelopathy rather than an encephalomyelitis?

DR. ALEXANDER SILVERSTEIN: Is this disease an Arthus phenomenon? If so, why not examine other viscera, especially the adrenal gland? Were the blood vessels thrombosed?

DR. GEORGE GAMMON: This is a disease induced by injecting a soup composed of tubercle bacilli and liquid petrolatum U.S.P. It is usually considered an allergic phenomenon. There are three documented studies, by Kabat, Ferraro, and Moyer, in which it was found that the development of this disease could be prevented with corticotropin. Our objective was to see whether we could alter the process once it developed. We treated animals with paralysis who had shown some degree of recovery and, although we could not get a complete reversal, since the causal agent was still present, there was a modification of the process. Corticotropin will act on the central nervous system in the same way it does on other tissues, as shown at the university in studies on the early treatment of transections of the spinal cord and on early treatment of experimental poliomyelitis.

DR. LOBACH: We treated one patient with the Guillain-Barré syndrome with corticotropin, but he grew progressively worse and died. Autopsy showed acute encephalomyelitis. A second patient with the Guillain-Barré syndrome was treated with corticotropin and recovered.

PHILADELPHIA NEUROLOGICAL SOCIETY; SECTION OF NEUROLOGY AND PSYCHIATRY OF THE MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, AND NEUROPSYCHIATRIC SECTION OF THE BALTIMORE COUNTY MEDICAL ASSOCIATION

Calvin S. Drayer, M.D.; Howell Inslip Hammer, M.D., and A. Earl Walker, M.D., *Presiding*

Joint Meeting, Nov. 7, 1952

Postoperative Seeding of the Subarachnoid Space and Ventricles from a Meningioma.

Dr. Nathaniel W. Winkelman Sr., Philadelphia.

The dissemination and eventual growth of neoplastic tissue within the subarachnoid space are characteristic of certain types of tumors, the most notorious being the medulloblastoma. Other tumors have this tendency, including ependymoma and malignant tumors of the nervous system. The recent test for brain tumor by examination of the centrifuged specimen of the spinal fluid gives evidence of the tendency for brain tumors to invade the subarachnoid space. Most of them, however, do not grow there.

The finding of meningiomatous growths within the subarachnoid space and ventricle is very unusual. Postoperative seeding is extremely rare. No case similar to the one reported has been found in the literature.

The patient had had a meningioma of the sphenoidal ridge for six years prior to operation. The patient survived for four years, and autopsy revealed numerous small duplicates of the original tumor within the subarachnoid space and in the ventricles, especially the fourth.

The case history and microscopic findings of the central nervous system were given. Lantern slides showed the implantations and growth of these seedings throughout the ventricles and subarachnoid space. An explanation of the mechanism was attempted.

DISCUSSION

Dr. Francis M. Forster, Philadelphia: The first question is whether these tumors were actually seeded, or whether this finding, by any chance, could have been an artifact produced at the time of sectioning the brain. A point against this idea is the sharp focus on both the surrounding tissue and the tumor in the section showing the cerebellum. It would be difficult to believe that this small patch of tumor tissue was inadvertently carried there.

I wonder whether Dr. Winkelman has any explanation of why these small tumors remained apparently the same size, or grew only slightly, during the four years.

The third question is whether these tumors could be meningiomas of multiple origin. Meningiomas arise in the ventricle infrequently, but usually in the lateral ventricle; the fourth ventricle would be a most unusual site.

The fourth question is whether or not surgical intervention played any part in the spread, how this tumor spread into the ventricle, whether there were any other tumors, etc.

We should pay tribute to a father-and-son team, each member carrying on his own investigation on the spread of tumors of the central nervous system.

Dr. Sanon: These tumors, especially meningeal tumors, which on section appear identical, behave very differently on culture. I was very much interested in this case because tumors like this, which appear to be of classic type, will in tissue culture behave very differently. Some will grow like fiberglas,* and others will actually reproduce the moment life appears in the culture. Likewise, these tumors sometimes grow extremely rapidly and present a typical mycosis. I had such a case only last week. The tissues are extremely resistant to trauma, so that if they are left at room temperature and then cultured, and the next day are placed in an ice chest for 48 hours—and I have repeatedly done that—they will grow. Some of them, even the classic types, are occasionally proteolytic.

I have always been amazed that meningiomas do not more frequently show invasion; I believe that these cells can remain dormant for quite a while and then start to grow.

Dr. Nathaniel W. Winkelman Sr., Philadelphia: The question Dr. Forster asked is one I had in mind too, i. e., the question of whether the tumor seedings were large enough to be of

four years' duration. Of course, a meningioma grows very, very slowly, and it is possible in four years to have tumors of varying sizes. We do not often see them very large; we have seen them about the size of a small lemon with a history of perhaps 20 years' duration. So if just a few cells were loosened, the little growths I showed might well have a four years' duration.

Our sections were taken in such a way that it is impossible for tumor tissue to be carried in by knife. The sections of the tumor, the sections of the medulla and cerebellum, and large sections of the brain were all made separately.

I think this is a type of tumor that was carried into the ventricles at some point. I have incriminated the surgical procedure. I may be wrong, but that is the only way I can think of. It happens in other cases, and it could here, with, as I said, no discourtesy to the surgeons.

Report of One Hundred Carotid Angiograms Taken with the New Contrast Medium Acetrizoate (Urokon®) on Chamberlain's Biplane Stereoscopic Angiographic Unit.
DR. PAUL LIU (by invitation), DR. FREDERICK MURTAGH, DR. HENRY T. WYCIS, and DR. MICHAEL SCOTT, Philadelphia.

In the past 10 months we have used the new contrast medium sodium acetrizoate (solution urokon® sodium 30%) in making all our carotid angiograms on the Chamberlain biplane stereoscopic sequence angiographic unit. We found that this new contrast medium compared favorably with iodopyracet (diodrast®) and was less irritating clinically than the latter. Use of the Chamberlain unit was found to be very desirable, since but a small amount of contrast medium was needed for a complete angiographic study of the carotid system.

One complication, namely, transitory unconsciousness with no neurological sequelae, was present in our series of 100 consecutive carotid angiograms. We found also that 50% of all our angiograms were of diagnostic value and 44% were reported as normal. False negative interpretations of the angiograms were made in 12% of cases.

DISCUSSION

DR. JOHN DE CARLO JR., Baltimore: I have not used acetrizoate for cerebral arteriography, but have used it for intravenous pyelography and find that it is definitely less toxic than other radiopaque substances. The department of radiology of Johns Hopkins Hospital is now using acetrizoate for angiocardiography and appears convinced that it is less toxic and produces fewer reactions. While perhaps a larger series of acetrizoate cerebral angiograms may be indicated, I believe that, in the light of this paper, acetrizoate is the present-day No. 1 contrast medium for cerebral arteriography. The authors are to be complimented on their fine presentation.

DR. WILLIAM THORNTON SPENCE, Washington, D. C.: Dr. Frank Walsh, at a scientific assembly in Washington about a year ago, stated that he had seen many cases of severe visual deficiencies secondary to angiography. I think he indicated iodopyracet in particular.

I had a case of hemiparesis, with possibly some visual loss. In my case the cause was iodopyracet and thrombosis of the internal carotid artery. I opened the internal carotid artery in the neck and sucked out some soft clot but never had sufficient back bleeding to produce any particular improvement.

The authors have reported the appearance of a flush with acetrizoate. We see that to a striking degree with iodopyracet, and to me that means irritation. I have always preferred thorium dioxide, and I have used it 10 or 12 years, with two or three injections of 5 cc. each, as rule not more than that.

The Council on Pharmacy and Chemistry of the American Medical Association determined that 25 cc. of thorium dioxide had an amount of radiation the equivalent of 0.5 to 1 γ of radium. If only 10 or 15 cc. is used, the dose is reduced to the equivalent of 0.2 or 0.5 γ. In the entire medical literature there have been five cases of tumor in persons who received thorium dioxide injections.

It is my feeling that this drug is the least irritating, and the authors have borne out that idea in their conclusions. Therefore, if it is possible to use a small amount with a machine such

as Dr. Chamberlain's, with which only the one injection is needed, it is still my feeling from my own experience that thorium dioxide is safest. However, I am delighted to hear about the acetrizoate, and I certainly intend to use it.

Neurol Toxicity in Tuberculous Patients Treated with Isoniazid. Dr. Geraldine King (by invitation), Dr. Frank W. Burge (by invitation), and Dr. George D. Gammon, Philadelphia.

In a series of 408 patients with advanced pulmonary tuberculosis treated with isoniazid (pyriziden®), 46 exhibited signs of a peripheral neuropathy not previously reported with this drug.

Fourteen patients were examined in detail. They had symptoms of numbness and tingling of the feet, and occasionally of the hands also, with spread up the extremities. Sometimes they experienced pain and muscle soreness, and occasionally a sense of unsteadiness or weakness.

Examination revealed sensory and, to a less degree, motor involvement distally, with decreased touch, pain, and temperature sensibility in the feet, progressing to decrease or loss of these modalities to the knees. In patients most severely affected, reflex changes consisted of decrease or loss of the Achilles reflex and increase or decrease of the patellar reflex. Weakness was absent or minimal.

The literature of toxicity was reviewed briefly, and, although this syndrome had not previously been reported, toxic symptoms were observed in the range used here, which was 4.5 to 13.5 mg. per kilogram a day (only four received less than 8 mg.).

These signs and symptoms cleared fairly promptly with withdrawal of the drug, if they were not allowed to progress too far; in these recovery was slow. This neuropathy puts a limitation on therapy with higher doses of this drug.

DISCUSSION

Dr. Frank W. Burge, Philadelphia: With large doses of isoniazid, 60% of patients with positive sputums came to have negative sputums. Inhalation of the dry drug with a DeVilbiss No. 175 powder nebulizer produced sputum conversions in 25% of patients who did not show conversion with oral dosage.

We have had some sputum conversions with isoniazid therapy in patients who had not had negative sputums in 10 or 15 years.

Ansotomy in Paralysis Agitans. Dr. Ernest A. Spiegel and Dr. Henry T. Wycis, Philadelphia.

In attempts to influence the tremor of paralysis agitans, interruption of afferent pathways in the midbrain tegmentum did not diminish the tremor. Reduction of the impulses passing from the thalamus to the striopallidum by thalamotomy had, at the most, only a slight effect for a few days. A definite diminution of the tremor could be obtained by lesions placed in the ansa lenticularis (ansotomy). For interruption of the pallidofugal fibers, Russel Myers entered the third ventricle and incised its lateral wall. He considers the risks of this operation too great to warrant its general employment. We therefore used the stereotaxic technique, inserting the electrodes through the frontal lobe in a direction from anterodorsal to ventrocaudal, so that the tip of the electrode reached the base of the globus pallidus. With the stylet electrode, lesions were placed in medial and lateroposterior directions, sometimes also laterally. A preliminary account of three cases is given. In the first case, that of a woman aged 40, ansotomy on the left side nearly abolished the tremor of the right side without impairing voluntary movements or producing pyramidal signs, disturbance in sensation, or alteration in muscle tonus. The improvement has been maintained for the observation period (four months; motion-picture demonstration). In the second case the favorable effect upon the tremor lasted three to four days only. In the third case the amplitude of the tremor of the left hand was definitely reduced by ansotomy on the right side and its frequency from 4.6 to 4.0 per second. Alternating flexor-extensor movements of the fingers could be performed more quickly on the left side (10 per 10 seconds) than on the right (7 per 10 seconds). Passive resistance to ventroflexion and dorsiflexion of the right hand, flexion of the elbow, and extension of the knee, and the cogwheel phenomenon were reduced.

DISCUSSION

DR. FRANCIS FORSTER, Philadelphia: It is a far cry from Wilson's early attempts to place electrodes in the globus pallidus of experimental animals to this report by the masters of stereothalamotomy, in their therapeutic approaches to this pathway to the globus pallidus, the ansa lenticularis. Their report is a preliminary one, and there are questions one would like to ask that only time will answer.

I wonder, as I know that Dr. Spiegel and Dr. Wycis do, whether these lesions actually are placed in the ansa lenticularis, but only time will tell us that. What was the difference between the second patient and the other two, in whom the therapeutic efficacy was short-lived?

On these questions, of course, we have to wait for further confirmation.

This approach differs from the operations which were geared to produce a motor weakness, and with the weakness a resultant decrease in involuntary movements. Even in those operations, however, there was always an element of time, and many of us, I am sure, recall patients who had sections of the lateral column and cord or cortical ablations and who for a considerable period seemed to improve, but as long as a year later had a marked recurrence of their symptoms. I know it is not fair to ask about the final result, because there has not been a sufficient interval of time.

I wonder also whether Dr. Spiegel and Dr. Wycis have been able to record any activity from the area ansa lenticularis and make any correlation from that.

I should also like to ask whether they think this procedure can be carried out bilaterally; and if not, why not?

DR. A. EARL WALKER, Baltimore: I notice the authors said that muscle tonus was improved, that the Parkinsonian rigidity was strikingly lessened. In the previous operations carried out for relief of tremor, such an improvement of muscle tonus has rarely occurred; if this procedure did nothing more than relieve the rigidity, it would be of great benefit to the patient.

DR. E. SPIEGEL, Philadelphia: In cases with bilateral involvement, it is planned to place lesions on the opposite side, in a second stage of the operation. The results of long-range observations and histological controls have to be awaited before definite conclusions can be drawn. The effect upon the muscle tone was contrary to expectations. In only one of the cases was the resistance to passive movements increased. The decrease in tone in Case 3 was particularly marked in the flexors of the left hand. Simultaneous recordings of the electroencephalogram, the electropallidogram, and the electromyograms of the affected muscles during operation, with local anesthesia, before ansotomy showed that the rhythmic bursts in the affected muscles are not accompanied by corresponding fluctuations in the cortex or the pallidum. However, one finds regular rhythmic discharges from the globus pallidus, so that this ganglion can hardly be severely impaired. A preliminary working hypothesis is outlined. It assumes that the tremor rhythm originates in the nucleus motorius tegmenti (reticulate substance of the rhombencephalon) and that the substantia nigra normally inhibits this mechanism, while centrifugal fibers from Area 6 synapsing in the pallidum and continued by pallidofugal fibers send facilitating impulses to the tremor-gentic center in the reticulate substance. This hypothesis is able to explain the production of tremor by a degeneration of the substantia nigra, and its diminution by lesions of Area 6 or of pallidofugal fibers. The effect of section of the lateral column of the cord (Putnam) probably is due to lesions not of the pyramidal tract, but of adjacent or overlapping reticulospinal fibers.

Relief of Pain in Advanced Carcinoma by Prefrontal Injection of Procaine. DR. FRANCIS E. NULSEN and DR. FRANCIS GRANT, Philadelphia.

Early in 1952 Van Wagenen and Liu described procaine block of white fibers of the frontal lobe as a means of predicting the effect of prefrontal lobotomy. Three cubic centimeters of 2% procaine hydrochloride was injected deep into each frontal lobe through coronal trephine openings, with transient changes in behavior resulting in favorable cases. Adams, at the University of California, began to use larger amounts of procaine hydrochloride (up to 10 cc. of a 1% solution, injected bilaterally) in an attempt to produce a longer-lasting beneficial change in psychotic patients. A favorable alteration in psychotic behavior was produced in some patients for six weeks or longer.

It seemed likely that injection of procaine into the frontal lobe in fairly large amounts might be a useful method of relieving the intractable pain produced by extensive carcinoma in patients whose life expectancy seemed short, and in whom interruption of no single pain-tract would be adequate to cover multiple sources of misery.

Burr holes are placed bilaterally, just in front of the coronal suture and 5 cm. from the midline. The dura is opened and the pia-arachnoid is generously coagulated to obliterate the underlying subarachnoid space. Injection is carried out at the bedside at least 48 hours after the openings have been made, in the absence of any sedation, with the patient's pain complaints at a maximum. No. 20 lumbar-puncture needles of 10 cm. length are directed in the same sagittal plane as the trephination, at an area just in front of the sphenoidal ridge until the floor of the skull is encountered, at a depth of 8.5 to 9.5 cm. Each needle is withdrawn 1 cm., and 3 to 5 cc. of 2% procaine hydrochloride is injected. Needles are then withdrawn to a level of 4 cm. below the coronal suture, and additional injections are made. Next the needles are replaced in the same coronal plane with lateral deviation at a depth of 7 cm. for further bilateral injections. Thus, as many as six separate portions of the frontal lobes may be infiltrated with procaine, to a total volume of 30 cc. In practice, injections are continued only to the point where a striking change in sensorium is produced—unconcern about pain, euphoria, and disorientation. Such changes are sometimes produced with as little as 10 cc. In general, confusion clears in a few hours; the patient usually begins to eat voraciously, and pain is not complained of for two or three days. Two to four separate treatments are usually undertaken on alternate days. Patients have not been incapacitated by treatment; their nursing care promptly becomes simpler. Five of six patients remained comfortable from four to nine weeks after injections. Three of these terminal-stage patients could be cared for at home without sedation. The other two required continued hospital care because of the underlying disease, but were cheerful without sedation. One died of peritonitis one week after injection.

We have no information concerning the mechanism by which prefrontal injections of procaine produce an effect similar to that obtained by surgical lobotomy. Two postmortem specimens have been obtained. In neither case was there gross evidence of significant destruction of the frontal lobe. Preliminary microscopic studies have failed to show cellular changes in the cortex or thalamus. It is conceivable that similar volumes of saline might produce the same effect.

Empirically, the method seems of value in the management of short-term pain problems. The cumulative effects of treatment permit gradual accomplishment of an ideal lobotomy result —relief of suffering without severe blunting of personality or deterioration.

DISCUSSION

DR. JONATHAN WILLIAMS, Washington, D. C.: I am not personally familiar with this technique. The duration of relief from one injection is puzzling. The more soluble hydrochloride salt of procaine is extremely diffusible, and not without danger if deposited in the ventricular system.

In cases of pain my preferred treatment is transorbital lobotomy. It is simple and safe, and with it the necessity is avoided of shaving the head, an undesirable thing, particularly in a woman who has so little time to live and regrow her hair.

The first case well illustrates the hypothesis that the effectiveness of lobotomy depends on quantitative interruption of fibers. As more procaine was added, more relief was obtained. I wonder whether saline would do the same thing.

DR. FRANCIS E. NULSEN, Philadelphia: Just the proper amount of destruction in the transorbital lobotomy would certainly be preferable to this rather elaborate procedure. As we have been doing these injections we also have been doing surgical lobotomies of a limited sort, and it makes a striking contrast to have a patient who has little pain as a result of a procaine injection, to which one can add and make her comfortable; to have in the next bed a patient who, unexpectedly, is deteriorated after a surgical lobotomy of limited extent, and, finally, to have in the next bed a patient who is fairly intact after a surgical lobotomy, only two weeks later to have her begin to complain of her pain again and one wonders what one can do next.

The main reason for feeling that this treatment might be worth while is not that it is simpler than introducing an ice pick, but that it is something one can do in a graded fashion.

PHILADELPHIA PSYCHIATRIC SOCIETY

Hugo Mella, M.D., *President, in the Chair*
Regular Meeting, March 13, 1953

Results to Be Effected with Psychoanalysis. Dr. Clarence P. Oberndorf, New York.

It is impossible to give an evaluation of results with psychoanalysis because no definition of psychoanalysis can be formulated that is acceptable to the majority of members of the American Psychoanalytic Association, which is the authoritative body of psychoanalysis in this country. It is also difficult to say where suggestive and educational psychotherapy, psychoanalytic psychotherapy, and "true psychoanalysis" begin or end, for they merge imperceptibly into one another.

Deviations of Freud's followers from his so-called classic psychoanalysis began early in this century and have continued up to the present time, giving rise to numerous schools. I am sure that each of these schools using some form of psychoanalysis, which might not be considered psychoanalysis by other schools, can claim good results.

The statistical method of evaluation is practically worthless because of the great number of variables in any psychotherapeutic or psychoanalytic procedure. The speaker suggested a candid pooling of experience by senior psychoanalysts and pointed out that weaknesses in psychoanalytic therapy might be eliminated if more frequent consultation were instituted in psychoanalysis. He stated the belief that it should become a custom that when a patient has been in classic psychoanalysis for 200 hours or in psychoanalytic psychotherapy for three years his case should be reviewed in seminar form with three senior analysts, for all analysts, including the speaker, have their unavoidable blind spots.

Area of Support Therapy. Dr. Edward A. Strecker.

There are a number of areas in psychiatry to which, for reasons of expediency and time considerations and because of the nature of the problems, formal psychoanalysis is not practical. Some of these areas are situations in which the important conflictual material is close to the surface, even though it may have deeper roots; situations which are definitely chronic and which no modern method of therapy can completely resolve (the patient can be much improved by being dealt with in a supportive manner); and situations in which the difficulty is mainly on the basis of recent and serious environmental insults. Support therapy begins with the first contact with the patient and takes advantage of every opportunity presented, beginning with the physical examination. Its chief facets are the physical examination, reassurance, occupational therapy, avocations and hobbies, the management of hostility, and the control of transference. Support therapy is not a good name, because it suggests merely patting the patient on the back. It would be preferable to speak of it as general therapy. Like any other therapy that is worth its salt, it must make a considerable penetration into the conflictual material. The author pointed out some of the differences between general psychiatric therapy and psychoanalysis.

Psychosurgery. Dr. Walter Freeman, Washington, D. C.

Since 1936 Dr. Watts and I have performed more than 2,000 lobotomies. In this paper are compared the results of 702 prefrontal lobotomies, performed mostly by Watts, and 1,302 prefrontal lobotomies, performed mostly by myself. The patients have been followed carefully, with the following results:

The operative mortality is twice as high in prefrontal as in transorbital lobotomy. Later fatalities are higher in the patients with prefrontal lobotomy, largely as the result of cardiovascular trouble, whereas in the transorbital group a large number of fatalities have resulted from malignant disease, for which relief from pain was attempted.

Physical complications, such as epilepsy, persistent incontinence, and obesity, are 20 times as high after prefrontal lobotomy as after transorbital lobotomy. Social complications, particularly the "frontal lobe syndrome," are found at least 10 times as frequently after prefrontal lobotomy. The incidences of other complications, such as alcoholism, illegitimate pregnancy, and suicide, are approximately equal in the two groups. It would appear, therefore, that transorbital lobotomy should replace the major operation.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

FUNCTIONAL RESTORATION OF THE PARALYZED DIAPHRAGM FOLLOWING THE CROSS-UNION OF THE VAGUS AND PHRENIC NERVES. J. O. BROWN and V. P. SATINSKY, Am. J. M. Sc. **222**:613 (Dec.) 1952.

Attempts were made to establish independent breathing movements of the paralyzed diaphragm by means of intrathoracic cross anastomosis of the vagus and phrenic nerves in dogs. It was found that the animals could survive if one-half the diaphragm was functioning. From 15 to 138 days after the anastomosis of the vagus to the distal segment of the phrenic nerve, it was found that the previously paralyzed half of the diaphragm was functioning synchronously with the normal portion of the diaphragm. There appeared to be anatomical continuity between the vagus nerve and the segment of the phrenic nerve to which it had been sutured. Further, the anastomosed nerve that had innervated one-half the diaphragm was able to maintain adequate respiration when the opposite phrenic nerve was cut.

BERLIN, New York.

THE HYDRIODIDE OF DIETHYLAMINOETHYLESTER PENICILLIN-G, NEOPENIL: III. UNUSUALLY HIGH PENICILLIN CONCENTRATIONS IN CEREBROSPINAL FLUID FOLLOWING INTRAMUSCULAR ADMINISTRATION. N. H. SCHIMMEL, W. W. WILSON, W. V. MATTEUCCI, and H. F. FLIPPIN, Am. J. M. Sc. **224**:247 (Sept.) 1952.

Doses of 500,000 units of neo-penil® (the hydriodide of diethylaminoethyl ester of penicillin G) and other depot penicillin preparations were administered to 28 patients with neurosyphilis, to determine the relative blood and spinal fluid concentrations of these penicillins. It was found that the spinal fluid concentration of penicillin following administration of neo-penil® was about 10 times as great as the concentration obtained with other types of penicillin. The plasma level following neo-penil® was equal to that obtained with procaine penicillin.

BERLIN, New York.

INTRACELLULAR DISTRIBUTION OF DIPHOSPHOPYRIDINE NUCLEOTIDE-CYTOCHROME *c* REDUCTASE AND CYTOCHROME *c* OXIDASE IN MAMMALIAN BRAIN. T. M. BRODY, R. I. H. WANG and J. A. BAIN, J. Biol. Chem. **198**:821, 1952.

Sucrose homogenates of rat liver and brain were separated into nuclear, mitochondrial, and microsome fractions by differential centrifugation. Spectrophotometric assays showed that cytochrome-*c*-oxidase activity was concentrated in the mitochondrial fraction from both tissues. Diphosphopyridine nucleotide-cytochrome *c* reductase activity was greatest in the mitochondrial fraction from brain, in contrast to liver, in which it was highest in the microsome fraction.

PAGE, Cleveland.

ROLE OF COENZYME A AND DIPHOSPHOPYRIDINE NUCLEOTIDE IN OXIDATION OF PYRUVATE. J. W. LITTLEFIELD and D. R. SANADI, J. Biol. Chem. **199**:65, 1952.

The single-step oxidation of pyruvate by diphosphopyridine nucleotide in the presence of coenzyme A has been studied. The product of the reaction was isolated and shown to be acetyl coenzyme A. Thus, at least four cofactors are required for pyruvate oxidation, namely, diphosphopyridine nucleotide, coenzyme A, Mg^{++}, and cocarboxylase.

PAGE, Cleveland.

ACETYLCHOLINESTERASE: XIII. REACTIVATION OF ALKYL PHOSPHATE-INHIBITED ENZYME. I. B. WILSON, J. Biol. Chem. **199**:113, 1952.

In a previous paper it was shown that the inhibition of acetylcholinesterase caused by tetraethylpyrophosphate, while irreversible by dialysis or dilution, could be reversed rapidly by reaction with hydroxylamine or choline and very slowly by reaction with water. The mechanism of inhibition parallels the mechanism of normal enzyme activity but differs greatly

in the quantitative aspects. A reversible enzyme-inhibitor addition complex, involving a covalent bond (coordinate) between the basic group of the esteratic site and the electrophilic phosphorus atom of the inhibitor, is initially formed. There follows a transfer of a proton from the acid group to an oxygen or halide atom simultaneously with a basic attack upon the phosphorus atom, resulting in the splitting out of a halogen acid, phenol, or phosphate molecule. As a consequence, a relatively unreactive phosphoryl enzyme is formed. During the normal activity of the enzyme, i. e., during the hydrolysis of carboxylic esters, an acylated enzyme is formed, but this intermediate reacts rapidly with water to form an acid and regenerate the enzyme. Phosphoryl enzyme, on the other hand, reacts only very slowly with water; it is the slowness of this reaction which makes these phosphate esters inhibitors rather than substrates. It is not, in the case of halophosphates and pyrophosphates, the ester linkage which is split.

The energy of activation for hydroxylamine reactivation of enzyme inhibited by tetraethylpyrophosphate is 7.0 Cal. per mole and for choline reactivation 14.5 Cal. per mole. The anionic site is preserved in the inhibited enzyme, and hence choline reactivation shows a saturation with respect to choline concentration and reactivation can be inhibited by tetramethylammonium and trimethylammonium ions, which are inhibitors of the normal enzyme. Phosphorylation of the basic group in the esteratic site sterically interferes, however, with binding at the anionic site. Tetraethylpyrophosphate and diethyl fluorophosphate yield equally reactive inhibited enzymes, but diisopropyl fluorophosphate yields a much less reactive phosphoryl enzyme. Compounds containing amino, pyridyl, guanidino, amidino, hydroxyl, or mercaptyl groups may be effective reactivators.

PAGE, Cleveland.

BIOGENESIS OF HISTAMINE. R. W. SCHAYER, J. Biol. Chem. **199**:245, 1952.

The data show that exogenous histamine cannot be detected in the blood, lung, kidney, intestine, or liver four hours after injection. The level of histamine employed, 0.05 γ per gram of body weight, is probably many times as great as the histamine level produced by an injection of 2 γ of L-histidine per gram of body weight. Thus it is probable that exogenous histamine is not a source of bound histamine. After administration of a single dose of C^{14}-L-histidine, minor in magnitude as compared with dietary and protein histidine, C^{14}-histamine is found for long periods in organs known to be rich in bound histamine. The following sequence of events is probable: Shortly after absorption of L-histidine into the blood stream the concentration of free histidine is highest, and in those organs containing histidine decarboxylase histamine is produced at a maximum rate. If the histamine is formed within cells possessing a binding mechanism, it may be retained in stable condition for long periods. Most of the histamine, however, is evidently formed in cells lacking a binding mechanism. It is therefore treated as exogenous histamine and undergoes further metabolism; a small percentage is excreted unchanged in the urine. Thus, bound histamine is rapidly built up in the organs, and relatively large amounts of histamine appear in the urine shortly after administration of L-histidine. Histamine production is probably proportional to free histidine concentration, a conclusion supported by the rough proportionality of urinary C^{14}-histamine to total urinary C^{14}.

PAGE, Cleveland.

BIOCHEMISTRY OF THE SPHINGOLIPIDES: VII. STRUCTURE OF THE CEREBROSIDES. H. E. CARTER and F. L. GREENWOOD, J. Biol. Chem. **199**:283, 1952.

In the catalytic reduction of hexaacetylphrenosin, acetic acid, but no reducing sugar, is formed. The reduction product yields a mixture of sphingine and dihydrosphingosine on hydrolysis. These data establish that in the phrenosin molecule galactose is attached to the terminal carbon atom of sphingosine.

PAGE, Cleveland.

MIGRATION DURING HYDROLYSIS OF ESTERS OF GLYCEROPHOSPHORIC ACID: III. CEPHALIN AND GLYCERYLPHOSPHORYLETHANOLAMINE. E. BAER, H. C. STANCER and I. A. KORMAN, J. Biol. Chem. **200**:251, 1953.

The investigation of the structure of the lecithins and cephalins (phosphatidylethanolamines) from natural sources gave rise to the question whether the phosphoric acid in these substances

is attached to the α or to the β carbon atom of the glycerol moiety. Since the acid and alkaline hydrolysis of natural lecithins yielded mixtures of α- and β-glycerophosphoric acid, it was assumed that they existed in the α as well as the β, form. The subsequent isolation of optically active lecithins was irrefutable proof of the occurrence of the α form. Doubt of the existence of the β form arose with the growing suspicion that the β-glycerophosphoric acid is an artifact, presumably formed by the migration of phosphoric acid. It has been shown that both the acid and the alkaline hydrolysis of cephalins and of their glycerylphosphorylethanolamine moiety is accompanied by a reversible migration of phosphoric acid. The hydrolysates of L-α-cephalins and of L-α-glycerylphosphorylethanolamine contain predominantly α-glycerophosphoric acid when obtained by acid hydrolysis and approximately equal amounts of α- and β-glycerophosphoric acid when obtained by alkaline hydrolysis. The α-glycerophosphoric acid is either partially (alkaline hydrolysis) or almost totally racemized (acid hydrolysis). There is evidence that the reaction schemes describing the acid and alkaline hydrolysis of the lecithins and of glycerylphosphorylethanolamine, are valid also for the cephalins and glycerylphosphorylethanolamine, provided that ethanolamine is substituted for choline. The occurrence of the migration of phosphoric acid makes it highly probable that most, if not all, of the β-glycerophosphoric acid in the hydrolysates of natural cephalins is formed by this reaction, and not by the hydrolysis of β-cephalins. Thus, contrary to general belief, the natural occurrence of β-cephalins, like that of β-lecithins, remains hypothetical.

PAGE, Cleveland.

ON EYEDNESS IN HOMONYMOUS HEMIANOPIA. F. S. ROTHSCHILD and M. STREIFLER, J. NERV. & MENT. DIS. **116**:59 (July) 1952.

Seven patients with homonymous hemianopsia were examined to determine their eyedness. The method of testing for eyedness consists of focusing on an ink spot in the center of a mirror so that the spot appears exactly on the tip of the nose. Then the two eyes are closed alternately. When the dominant eye is closed, the spot moves from the tip of the nose toward the closed eye. When the subordinate eye is closed, the ink spot remains in place. By this method it was found that eyedness was homonymous to the hemianopsia, i. e., the right eye was dominant in right homonymous hemianopsia and the left eye in left homonymous hemianopsia. The authors postulated that this is an attempt to reestablish the relation between body and visual space by the formation of a pseudofovea and the establishment of the dominance of the eye homonymous to the hemianopsia.

BERLIN, New York.

WOUNDS OF THE VISUAL PATHWAY: I. THE VISUAL RADIATION. J. M. K. SPALDING, J. Neurol., Neurosurg. & Psychiat. **15**:99 (May) 1952.

The author reports the defects in the visual field which follow injuries to the optic radiation in man and describes the anatomical deductions which can be made from them, with particular reference to the anterior half of the radiation.

Spalding reviewed a series of 958 cases of penetrating head injury, mainly gunshot wounds. In 188 of these there was a visual field defect attributable to injury to the visual radiation or striate cortex. His conclusions are based on the 62 of these cases in which injury was confined to the visual radiation.

It was found that wounds involving the upper or the lower margin of the anterior part of the visual radiation cause partial quadrantopsia in which the horizontal meridian is spared and the field defect projects toward the fixation point in the vertical meridian. Wounds involving the intermediate part of the anterior radiation cause narrow, sector-shaped defects in the horizontal meridian reaching to the fixation point.

It follows that in the anterior radiation fibers subserving central vision lie on the lateral aspect, tending to congregrate at the intermediate part, and fibers subserving peripheral vision lie on the medial aspect, tending to congregate at the upper and lower margins. This arrangement, the author points out, though contrary to previous beliefs, is in accord with both experimental and clinical evidence.

ALPERS, Philadelphia.

Psychiatry and Psychopathology

BLOCKING AS PRIMARY SCHIZOPHRENIC DISORDER. VICENTE P. CABELLO, Rev. asoc. méd. argent. **66**:92 (April-May) 1952.

Pereyra and his school in Argentina have emphasized blocking as a fundamental disorder in schizophrenia. It interferes with thinking, feeling, and acting. It affects every act which involves free will and decision of the patient. It is most readily demonstrated objectively in thinking. It manifests itself as blocking in speech. Subjectively, it is the cause of perplexed states and loss of self-control. From the affective standpoint, it is observed as apathy, loss of interest, disinclination to work, and even stupor. It accounts for lack of direction and affects contact of the individual with the external world. This blocking is definitely organic, and not psychogenic.

N. SAVITSKY, New York.

Meninges and Blood Vessels

CEREBRAL ANGIOGRAPHY: ITS VALUE IN THE DIAGNOSIS OF VARIOUS INTRACRANIAL AFFECTIONS. A. J. BELLER and E. PEYSER, Harefuah **43**:27 (Aug.) 1952.

Angiographic studies were performed in 80 cases over a period of three years—since 1950 by the percutaneous method alone. Angiography is most useful in the precise diagnosis of intracranial vascular lesions, such as aneurysm and vascular malformation. In cases of such lesions the clinical picture is often atypical, and diagnosis without laboratory aid is extremely difficult. In three of five cases of the sphenoidal-fissure syndrome the lesion was an aneurysm; in the other two it was a tumor. The only method of differential diagnosis in these cases was the angiogram. The apparent size of the aneurysm on the angiogram does not always correspond to its actual dimensions. Only part of the aneurysm may be filled with dye because of the formation of cyst-like structures at the site of bleeding. Only extradural aneurysms reach a large size; subdural aneurysms within the subarachnoid space rupture early. The authors report two cases of aneurysms in the anterior communicating artery in which diagnosis could be made only by angiogram. They cite the case of an arteriovenous malformation of the cerebral cortex with a history of Jacksonian attacks in a man aged 30. The electroencephalogram showed a focus in the left frontotemporal region. The veins and the arteries filled at the same time, without a capillary phase. In another case, one of traumatic carotid sinus fistula, the carotid artery was enlarged. This was also true of other blood vessels of the brain. In a man aged 50 with a six-year history of Jacksonian attacks without loss of consciousness right hemiplegia appeared after a head injury four months before his admission to a hospital. The weakness of the right side and the aphasia improved. Angiography showed an occlusion of the left middle cerebral artery and enlargement of the ventricle on the same side, after pneumoencephalography. Though the clinical course suggested a tumor, angiography and air studies indicated the presence of vascular occlusion. In another case the clinical picture was that of vascular disease, but the lesion was a tumor pushing up the middle cerebral artery, with typical bowing of the anterior cerebral artery. The authors state that more recently they have been using angiography alone in the diagnosis of expanding lesions. Of 43 cases of tumor of the brain, in which angiography was done, the tumor was demonstrated by angiography alone in 50%.

N. SAVITSKY, New York.

LOCALIZED TUBERCULOUS ENCEPHALITIS. D. FURTADO, O. CARVALHO and M. FERREIRA, Arq. neuro-psiquiat. **10**:315 (Sept.) 1952.

The authors note the rarity of recovery from localized tuberculous encephalitis in the days before antibiotic therapy. A case is reported in which the focus was removed surgically with apparent success.

A woman aged 46 was admitted to the hospital with a history of left-sided Jacksonian attacks for two years. For four months before admission a left-sided weakness appeared and increased. There was no personal or family history of tuberculosis. Examination on admission showed a blood pressure of 120/80; the physical and gynecologic examinations were noncontributory.

There were bilateral papilledema, weakness of the left lower part of the face, complete left hemiplegia, with hyperreflexia and Oppenheim, Babinski, and Hoffmann signs on the left. There were no sensory changes. Some rigidity of the neck was noted, and a Kernig sign was elicited on both signs. Lumbar puncture was not attempted because of the papilledema. An angiogram showed pushing down of the anterior choroidal artery. An electroencephalogram suggested the existence of an expanding lesion in the region of the Sylvian fissure. An operation was done eight days after entrance. The brain tissue in the region of the right frontal cortex was found to be harder than normal, with small yellowish granular structures. Brain tissue removed for biopsy showed cellular filtration, necrotic areas, and giant cells. The patient was given streptomycin, 2 gm. a day, for three months. The attacks diminished only for two months, with no change in the paralysis. They then became more frequent, with a frequency up to two or three a day, the longest interval being only eight days. Loss of consciousness followed some of the attacks.

The patient was readmitted to the hospital 10 months later. On this examination she complained of heaviness in the left limb. The paralysis of the left side was about the same; the fundi were normal. Weakness was greater in the lower limb, with some contractures. There was marked impairment of all modalities of sensation on the left side. The electroencephalogram showed disappearance of delta waves noted previously, especially on the right side. The amplitude of the waves on the right side was greater than that of waves on the left. A second operation was performed one month later, with wide excision of evidently altered brain tissue. Histologic diagnosis was tuberculous meningoencephalitis with considerable changes in the blood vessels. After the operation her convulsive attacks became fewer, and there was some improvement in motor power of the left upper extremity. Use of streptomycin was continued.

N. Savitsky, New York.

Diseases of the Brain

Lead Poisoning: Observations in Fourteen Cases. R. C. Giannattasio, A. V. Bedo, and M. J. Pirozzi, A. M. A. Am. J. Dis. Child. **84**:310 (Sept.) 1952.

In this series the commonest presenting symptoms were vomiting, abdominal pain, convulsions, and constipation. The diagnosis was made only if the index of suspicion was high. Infection of the upper respiratory tract or ear was present in 57% of the cases; its presence may be misleading. Hepatomegaly was present in 50%. There was definite evidence of encephalopathy in 10 cases; in 2 others there was coexisting tuberculous meningitis, so that the diagnosis of lead encephalopathy could not definitely be made. Convulsion, present in seven cases, was the outstanding encephalopathic symptom; lethargy, irritability, ataxia, ptosis, dragging of the foot, and tremors were also seen. Persistent vomiting commonly antedated the neurologic symptoms by several weeks. The urine contained sugar, acetone, and increased calcium. A clear cerebrospinal fluid with a positive reaction to the Pandy test and a normal or near-normal cell count should arouse suspicion. In the majority of cases there were over 1,500 basophilic stippled red blood cells per 1,000,000 red cells. A typical zone of increased density was seen in the metaphyses in every case. In all but one case there was over 0.1 mg. of lead per liter of a 24-hour specimen of urine; in this case there was 0.08 mg. per liter. Transient elevation of blood sugar was found in three cases; the serum phosphorus was reduced in three of the eight cases. The patients were placed on a regimen calling for a high calcium and phosphorus intake, large doses of vitamin D, calcium gluconate, sodium citrate, magnesium sulfate, and other sedatives. Two patients were treated with dimercaprol, 3 mg. per kilogram every four hours around the clock for 10 days. Both were left only with ptosis of the left eyelid. Of three comparable patients not treated with dimercaprol, one was discharged home blind, another died, and the third was discharged with left spastic hemiplegia and left facial palsy. Patients with tuberculous meningitis received streptomycin in addition. Only one of the remaining five, with mild encephalopathy, had a residual neurologic defect—tremors of the upper extremities.

Siekert, Philadelphia.

BRAIN ABSCESS—OTOGENIC AND RHINOGENIC. B. H. SHUSTER, A. M. A. Arch. Otolaryng. **56**:114 (Aug.) 1952.

At present most intracranial complications of otolaryngologic origin are associated with chronic, rather than acute, infection of the ear or sinuses. Among the intracranial complications of ear and nose infections, brain abscess is probably as common as any of the others, and Shuster considers this subject in the present paper.

He first points out that the otolaryngologist who first sees the patient should keep the possibility of such a complication in mind and learn to recognize it. Of the signs or symptoms of brain abscess the most striking is probably the mental status of the patient. He is listless and unmindful of his surroundings. The characteristic headache is dull and thumping. The pulse rate is usually slow, and an elevation of temperature may occur with a subnormal pulse. Mild papilledema may be present. There may be a moderate increase in cell count of the spinal fluid.

In looking for localizing signs, the otolaryngologist should be acquainted with the anatomic features in the areas usually involved. The temporal lobe, the cerebellum, and the frontal lobe are the areas involved when the ear or sinuses are the etiologic factors. The temporal lobe is the commonest site. The author outlines points helpful in localization.

The treatment is surgical, and Shuster feels that the otolaryngologist, rather than the neurosurgeon, is best suited to continue the care of the patient and treat the abscess from the feeding point in the mastoid or sinus. From his experience, he finds that as soon as the abscess is diagnosed and localized, incision, drainage, and the insertion of a rubber tube constitute the simplest and most satisfactory method of treatment.

ALPERS, Philadelphia.

CALCIFICATIONS IN INTRACRANIAL NEOPLASMS. F. MARTIN JR. and L. J. LEMMEN, Am. J. Path. **28**:1107, 1952.

Martin and Lemmen found calcification in 207 of 1,577 intracranial neoplasms, or in 13.1%. Calcifications occurred in some instances of every type of tumor except the schwannoma and hemangioblastoma. Four patterns of calcification were differentiated.

Pattern 1: The calcification occurred as small globules in the adventitia or media of smaller vessels and the endothelium of capillaries. This was the commonest pattern, occurring in 93 tumors.

Pattern 2: Calcification similar to that in Pattern 1 involved adjacent blood vessels whose zones of necrosis overlapped, the result being a conglomerate mass of calcium. This pattern was uncommon and tended to be associated with glioblastoma.

Pattern 3. Calcium salts were deposited in an area of old hemorrhage or necrosis.

Pattern 4: This pattern was of several types: globules within tumor cells, globules within the stroma or capsule of the tumor, and globules at the margin of the tumor. Such changes were seen in 85 tumors, chiefly craniopharyngiomas.

FOLEY, Boston.

ABLATION OF ABNORMAL CORTEX IN CEREBRAL PALSY. W. PENFIELD, J. Neurol., Neurosurg. & Psychiat. **15**:73 (May) 1952.

Cerebral palsy may be defined, in a broad sense, as loss of function due to brain injury. Such injury may affect motor centers, producing spastic paralysis of an arm or leg, but it may also affect other areas of the brain and thus cripple other functions than those of arm and leg movement.

Penfield subscribes to the thesis that abnormal cortex incapable of useful service does in some cases exert a noxious influence upon the rest of the brain which might otherwise function normally.

In this paper he reviews operative procedures and results in patients with epilepsy, mental retardation, and spasticity. He concludes that patients who suffer from cerebral palsy may be benefited by cortical excision in various ways. However, he states they must be very carefully studied and selected before such radical procedures are to be considered.

The possible benefits follow: 1. The patient who is subject to recurring cerebral seizures may be relieved of his attacks. 2. The patient who has a discharging lesion of the cortex and

shows progressive mental retardation may be greatly improved by excision of the partially destroyed cortex, provided intellectual degradation has not gone too far. This applies particularly to children in the early stages of mental retardation and behavior abnormality. 3. Patients with severe hemiplegia from infancy may be freed from spasticity to a considerable extent by excision of the motor cortex.

In the experience of the author and his colleagues, complete hemispherectomy is rarely advisable. But subtotal hemispherectomy and the discriminating ablation of all nociferous cortex may bring great improvement to selected patients with cerebral palsy.

ALPERS, Philadelphia.

STUDIES IN TRAUMATIC EPILEPSY: FACTORS INFLUENCING INCIDENCE OF EPILEPSY AFTER BRAIN WOUNDS. W. R. RUSSELL and C. W. M. WHITTY, J. Neurol., Neurosurg. & Psychiat. **15**:93 (May) 1952.

Traumatic epilepsy has been a constant source of interest and after World War I gave rise to many special studies, both as regards the incidence of post-traumatic epilepsy and the clinical features of the fits. Russell and Whitty here present a review of a five-year follow-up study of 820 cases of brain wounds sustained during the 1939-1945 war from the standpoint of traumatic epilepsy.

The over-all incidence of epilepsy for this series is already over 43%, five years after the wound was incurred. In a 10-year follow-up study it is likely that this figure will be about 50%. This figure, despite great improvement in surgical technique and the avoidance of sepsis, is about the same as that reported from the 1914-1918 war cases. This would seem to indicate that progressive gliosis and scarring per se cannot provide an adequate explanation for the occurrence of traumatic epilepsy, as suggested by Penfield in 1927.

The interval after wounding at which the first fit occurred varied widely. There is no obvious explanation for this wide variation. The figures obtained in this series indicate that for frontal wounds the first fit tends to occur later than for wounds in other regions of the brain.

Previous writers have pointed out that the site of the brain wound affects the incidence of fits. The findings in the present study support a higher incidence for wounds in the central region, ranging from 65%, for the parietal lobe, to 38%, for the occipital lobe. Wounds lying within 5 cm. of the sagittal line were found to have a much lower incidence of epilepsy than wounds charted within the main outline of the skull. It also would appear that patients with more extensive wounds are only slightly more prone to the development of fits.

The authors discuss the possible anatomic and physiologic causes of traumatic epilepsy and offer a tentative explanation which would clarify the mechanism of fit production.

ALPERS, Philadelphia.

OLFACTORY-GROOVE MENINGIOMA WITH AN INVERTED FOSTER KENNEDY SYNDROME. DEJEAN, C. GROS, R. CAZABAN, and GASSENC, Rev. oto-neuro-opht. **24**:413 (Oct.) 1952.

The authors report the case of a man aged 49 in which a central scotoma and optic nerve atrophy were found on the side opposite a meningioma of the olfactory groove. The authors also note the paucity of findings, which were almost entirely ocular, in this case of a long-standing lesion. The symptoms began with diminished vision in the right eye. There were no symptoms during the next three years except for an occasional headache. Three years after onset, vision was diminished in the right eye, the right disk was slightly blurred, and the fields were normal. Two months later there was bilateral papilledema, vision was limited to perceptions of light only in the right eye, and it was less impaired in the left eye. The pupils were normal; a central scotoma was present, and central vision was absent for color in the right eye and was intact in the left eye. Pallor of the right disk was visible through the papilledema. The blind spot was enlarged in the left eye. There were concentric contraction of the visual field and a huge central scotoma for color and white in the right eye. Smell was not impaired, and the mental status was normal. The electroencephalogram and roentgenogram of the skull showed no abnormality. Ventriculography showed a pushing up of both anterior horns, especially on the left side. A meningioma of the olfactory groove the size of a mandarin orange was removed on the left side.

N. SAVITSKY, New York.

SPOTTY CEREBELLAR SYMPTOMATOLOGY: ITS DIAGNOSTIC SIGNIFICANCE. J. M. OBARRIO, Prensa méd. argent. **39**:1493 (July 4) 1952.

In 1934, in collaboration with Dowling and Pedacci, Obarrio described spotty cerebellar symptomatology as evidence of midline tumors of the cerebellum. In this paper, he reports 26 cases, 3 of them in detail. The tumors were all midline cerebellar growths, many of them in children. Cerebellar symptoms are bilateral and asymmetric, sometimes involving one upper extremity and the contralateral lower extremity in the same patient. The author emphasizes the clinical value of the contributions of André Thomas in the evaluation of cerebellar symptomatology. He notes especially the clinical significance of absence of resistance to passive movement in various joints.

N. SAVITSKY, New York.

Diseases of the Spinal Cord

TWO TYPES OF COMPRESSION OF THE CORD DURING THE COURSE OF CANCER OF THE LUNG. N. ROMANO and R. A. EPHERABIDE, Rev. asoc. méd. argent. **66**:212 (July) 1952.

Romano and Epherabide describe two types of cancer of the lung with metastases compressing the spinal cord and report a case of each. Both were of men aged 38 who were heavy smokers. The first type begins near the apex of the lung and invades the vertebrae by direct extension. In this type the diagnosis of primary tumor of the lung is usually easy. The seat of the vertebral involvement is usually the upper thoracic region (second to fifth thoracic vertebrae). In this type there is usually no involvement of other bones. In the second type the diagnosis of the primary pulmonary site is often very difficult, the neoplasm sometimes being only very small nodules which cannot be detected clinically. There are usually widespread metastases to other bones; the lower thoracic and the lumbar vertebrae are most frequently involved.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

PATTERNS OF SENSORY DISTURBANCES IN THE TRUNK AND FACE IN POLYNEURITIS. N. SAVITSKY and E. SAVITSKY, J. Nerv. & Ment. Dis. **115**:433 (May) 1952.

In the presence of severe peripheral neuropathy, of various causes, sensory changes were observed on the trunk, in addition to the usual sensory loss in the extremities. There was impaired perception of touch and, to a less degree, of pain on either side of the midline, both anteriorly and posteriorly, of the trunk. These sensory changes correspond to the area of innervation of the distal fibers of the intercostal nerves.

BERLIN, New York.

ACCOMMODATION PARALYSIS DUE TO LEAD, WITH CHANGES IN VISUAL ACUITY FOLLOWING INGESTION OF FOOD. M. COLLIER, Rev. oto-neuro-opht. **24**:446 (Oct.) 1952.

A house painter aged 44 had complained of impaired vision for far and near for a few months. He was able to read for only a short time. Correction by lenses did not help the visual complaints. The pupillary reactions were normal; there was slight retinal arteriosclerosis; the central and peripheral fields were normal, and the intraocular tension showed no abnormalities. The ophthalmologic diagnosis was paralysis of accommodation. A few years before he had had what was probably lead colic. There was a definite history of exposure to lead without any effort to protect himself. Lead was found in the urine. There was no stippling and only 3,900,000 red blood cells. The author also reported curious improvement of vision for 1½ hours after eating.

N. SAVITSKY, New York.

A PHANTOM SUPERNUMERARY LIMB AFTER CERVICAL ROOT LESION. MACDONALD CRITCHLEY, Arq. neuro-psiquiat. **10**:269 (Sept.) 1952.

Critchley discusses phantom sensation in limbs which have not been surgically removed but which were rendered functionless by injury or disorder of nerve supply. Phantom sensation in cases of this type constitutes a phantom third limb, or even a phantom fourth limb in paraplegic patients. Mayer-Gross was the first to report a phantom limb after injury to the brachial plexus

(*Nervenarzt* **2**:65, 1925). Critchley suggests the term "phantom supernumerary limb" for the imaginary limb associated with hemiplegia, paraplegia, and lesions of the roots and plexuses. He reports one case in which there was extensive injury to the roots of the cervical plexus.

A man aged 22, during the early morning hours of June 14, 1951, collided with a motor car while riding his bicycle. There was complete amnesia from the time of his having breakfast until he recovered consciousness, 30 minutes later. He was confused for about a day. Soon after he regained consciousness, he complained of pain in his right upper limb and could not move it. There was also numbness of the right upper extremity, especially on the radial side of the hand. He also noted excessive sweating of the right hand and hypersensitivity of the palm to touch and heat.

The neurologic examination on Oct. 15, 1951, showed a Horner syndrome on the right; there were weakness and atrophy of the trapezius and sternocleidomastoid muscles on the same side, and wasting of the levator scapulae, the supraspinati and infraspinati, part of the pectoralis major, and the deltoid, biceps, triceps, forearm muscles, and hypothenar eminence. All movements of the right upper limb were impaired. Tonus was diminished in the right upper extremity; there was no fibrillation. The deep reflexes were not elicited in the right upper limb. There was diminished sensation on the outer side of the right forearm and hand and the right side of the neck. There was a fracture of the right clavicle in the middle of its shaft, without displacement. An electromyogram showed denervation of the muscles of the right upper limb except for the pectoralis major. The signs and symptoms were considered due to avulsion of the anterior roots of the third to the seventh and the posterior roots of the third to the sixth cervical spinal nerves. Surgical intervention was not advised.

During the first 10 days after the injury the patient thought that his paralyzed limb lay on his right side, when actually it was immobilized in a splint in an attitude of abduction to 90 degrees. It seemed to him that he could move the right upper limb normally, especially the right hand. When his own arm was moved passively, he did not feel that it was his own. After 10 days the phantom limb began to disappear and to merge with the paralyzed limb. For a while he "willed" the phantom limb to move whereupon it adopted the same position as the actual limb. After the first 10 days, on occasion, in dreams and for a short time after awakening, he would feel as though he could use the paralyzed limb. On one occasion, on getting up, he felt as though he had two arms which fused at the elbow to form a paralyzed forearm. As soon as he moved the left forearm, this impression of fusion disappeared.

While there was no clinical evidence of focal cerebral disorder during the time the patient was under observation, the author cannot exclude the presence of an abnormality of the parietal lobe during the first 10 days after the accident. It probably caused some disorder of the body image and contributed to the appearance of the phantom limb. N. Savitsky, New York.

Paralyses of the Last Four Cranial Nerves and the Cervical Sympathetic Fibers: the Villaret Syndrome. H. Roger and C. Raybaud, Arq. neuro-psiquiat. **10**:338 (Sept.) 1952.

Paralysis of the last four cranial nerves and the cervical sympathetic fibers on the same side was described by Villaret in 1916 in a gunshot wound. Roger and Raybaud report a somewhat unusual case secondary to infection of the neck. A Corsican gardener aged 64 was seen for a swelling in the neck and pain with swallowing. His pains radiated to the shoulder and the supraclavicular region on the same side. Examination showed a swelling in the parotid region, torticollis, and tenderness over the swelling; a prominence of the lateral wall of the pharynx displaced the left tonsil forward and inward. Operation was done; an incision of 5 or 6 cm. was made along the interior border of the left sternocleidomastoid muscle; pus was evacuated. One week later there was swelling of the left upper limb, lasting a few days. Twelve days later a fistula developed in the lateral wall of the pharynx. A second incision was followed by complete healing.

Soon after onset of the illness the patient had dysphagia with nasal regurgitation and attacks of coughing. For the first few weeks there was frequent vomiting toward the end of, and sometimes for half an hour after, meals. Neurologic examination showed evident involvement of the last four cranial nerves on the left side and the left cervical sympathetic fibers. There were

left palatoplegia, hypesthesia of the posterior part of the tongue, diminished taste sensation on the posterior half of the left side of the tongue, left laryngoplegia, laryngeal anesthesia, paralysis of the left trapezius, and atrophy of the left side of the tongue with deviation to the left. There was a typical Horner syndrome on the left side. Roentgenograms of the spine and skull revealed no abnormality. The authors note that in this case reflex coughing occurred on touching the left external ear. Cough was also produced by touching the external auditory canal, the retroauricular region up to the hair line, the angle of the jaw, and the inferior maxilla. This cough reflex, which was first described by Escat, is due to irritation of the vagus nerve. The authors also noted paralysis of the esophagus in this case; a barium meal went down very slowly (14 to 45 minutes) because of the absence of peristaltic movements.

N. Savitsky, New York.

Treatment, Neurosurgery

New Treatment for Hereditary (Huntington) Chorea. D. Goldman, Am. J. M. Sc. **224**:573 (Nov.) 1952.

The treatment of Huntington's chorea by oral administration of procaine amide is suggested by Goldman, who observed almost complete relaxation in a patient given procaine for dental work. Patients with Parkinsonism and myoclonic jerks showed little or no improvement as compared with the improvement in six patients with Huntington's chorea. Treatment generally was started with a dose of 0.25 gm. four times a day, and the amount was built up over a few weeks to 1.0 gm. four or five times a day. Intolerance was represented by some degree of faintness and somnolence, feelings of numbness or paresthesias in the extremities, and dryness of the mouth.

Foley, Boston.

Mephenesin in Treatment of Spasticity in Multiple Sclerosis. B. Libet and D. Rubin, J. Nerv. & Ment. Dis. **116**:198 (Sept.) 1952.

In 20 of 26 patients with multiple sclerosis who received 1.0 to 2.0 gm. doses of mephenesin in elixir form, there was a temporary reduction of spasticity. The effects were maximum 10 to 15 minutes after administration and subsided in 30 to 60 minutes. The chief usefulness of the drug was to facilitate physical therapy exercises in spastic extremities, but in some patients with the relief of spasticity there was also a reduction in power, so that they could not perform the exercises. The side-effects of the drug consisted of feelings of mild intoxication, euphoria, drowsiness, lassitude, weakness, and anesthesia of the tongue and buccal mucosa.

Berlin, New York.

Encephalography, Ventriculography and Roentgenography

Discography: Technique, Indications, and Evaluation of the Normal and Abnormal Intervertebral Disc. R. B. Cloward and L. L. Buzaid, Am. J. Roentgenol. **68**:552, 1952.

Discography is the term applied to the roentgenographic demonstration of the intervertebral disk by means of injection of a radiopaque material into the substance of the disk. The procedure was first described in 1950 by Lindblom, of Stockholm. Discography, when properly executed, has the advantage of much greater accuracy than myelography, not only in posterior herniations of the intervertebral disk but in lateral and anterior herniations, as well as herniations into the vertebral bodies themselves.

Cloward and Buzaid describe and illustrate their technique for the injection of 35% iodopyracet (diodrast®) into the intervertebral disk and show roentgenograms of normal and abnormal intervertebral disks. A normal disk usually requires less than 1 cc. of iodopyracet, and often considerable pressure on the syringe is required for injection. The normal disk is well limited to the intervertebral space in both the anteroposterior and the lateral projections. An abnormal disk can often be injected with as much as 5 cc. of iodopyracet, and the injection may require very little pressure on the syringe. Posterior herniations of the disk are the commonest, although

the discograms have disclosed a surprising number of anterior herniations. These may be present with or without an associated posterior herniation. Lateral herniations and unsuspected herniations into the bone of the adjacent vertebral body can also be demonstrated very clearly. Degenerated disks can be identified by a flattening of the disk space and extrusion of the disk material circumferentially. The authors feel that discography is not necessary for the diagnosis of degenerated disk, for the demonstration on plain films of a narrowed interspace with associated osteophyte formation is proof enough of the existence of such a lesion. Discography should help considerably in the diagnosis of unexplained low-back pain and in demonstrating the cause of failure of treatment of known posterior herniations of intervertebral disks. Discography may lead to improvement of present methods of treatment.

WEILAND, Grove City, Pa.

MYELOGRAPHIC DIAGNOSIS OF EPIDURAL METASTASIS IN THE LUMBOSACRAL SPINAL CANAL. B. S. EPSTEIN, Am. J. Roentgenol. **68**:730, 1952.

Epstein reports on the myelographic findings in 11 cases in which the final diagnosis was epidural metastasis in the spinal canal. The admission diagnosis in 9 of the 11 cases was herniation of the nucleus pulposus of the lower lumbar portion of the spine. The possibility of metastatic disease was considered in two cases because of a known tumor of the kidney in one and a tumor of the breast in the other. All the patients experienced intermittent low-back pain with sciatic radiation. Myelograms in 7 of the 11 cases showed a deformity of the distal end of the column of ethyl iodophenylundecylate (pantopaque®) which seemed characteristic of epidural metastasis. The caudal portion of the sac assumed a tapered appearance, resembling an inverted cone with the apex turned away from the lesion. In the other four cases the findings were considered compatible with, but not typical of, herniated intervertebral disk. Operative confirmation was obtained in 10 of the 11 cases. In the seven cases in which the defect was characteristic, the tumors were fibrosarcoma of the upper portion of the sacrum, two cases; angiosarcoma of the upper portion of the sacrum, one case; "benign metastasizing goiter," one case, and metastasis to the lumbosacral interspace from carcinomas of the kidney, sigmoid colon, and stomach, respectively, three cases. The metastasis from the stomach was not verified by operation, either on the stomach or on the spine. The tumors which produced the typical defects were fibrosarcoma, myeloma, and metastases from the breast and lung. In all cases the myelographic alterations appeared to be due to the epidural deposits of tumor tissue, rather than to visible pathologic distortion of the bony walls of the spinal canal. Plain roentgenograms of the spine which were made before the myelograms were believed to be negative or equivocal in 6 of the 11 cases.

WEILAND, Grove City, Pa.

News and Comment

LOS ANGELES SOCIETY OF NEUROLOGY AND PSYCHIATRY

Members of the Los Angeles Society of Neurology and Psychiatry are being invited by Dr. Robert E. Wyers and staff as guests of the Norwalk State Hospital, Norwalk, on April 15, 1953. Dinner will be served in the main dining room at 7 p. m., to be followed by the scientific program, at 8 p. m. Of interest will be actual case presentations.

Information may be obtained from the secretary, Philip J. Vogel, M.D., 1801 New Jersey St., Los Angeles 32.

TRAINING IN CHILD PSYCHIATRY

Approval has been granted by the Council on Medical Education and Hospitals of the American Medical Association and the American Board of Psychiatry and Neurology for a residency program in child psychiatry at the Emma Pendleton Bradley Home, an independent, dynamically oriented children's neuropsychiatric hospital, which is an associate member of the American Association of Psychiatric Clinics for Children. This program will provide for three appointments at a time, each of one year's duration. Preferably, those considering work here should already have had two years of approved psychiatric training with adults.

The Bradley Home has a patient population of 50 children from 4 to 12 years of age, of both sexes and of normal intelligence. Psychoses, neuroses, behavior disorders, both organic and psychogenic and convulsive disorders associated with emotional disturbances are represented. The work would involve the usual aspects of admission, diagnosis, and therapy, both with children and with the parents. Teaching conferences covering the field of child psychiatry would be arranged within the institution; in addition, special attention would be given to electroencephalography. The residents would be expected to take part in an active research program and to follow both independent and directed reading programs.

They would also participate, both as teachers and as learners, in the various approved training programs for other disciplines now being carried on at the Bradley home. These include clinical psychology, psychiatric social work, psychiatric nursing, teaching of exceptional children, and pediatric residencies.

Requests for further information from institutions and individuals may be addressed to Maurice W. Laufer, M.D., director, Emma Pendleton Bradley Home, Riverside 15, R. I.

FOUNDATIONS' FUND FOR RESEARCH IN PSYCHIATRY

The Social Research Foundation has made a grant of approximately $6,000,000 for psychiatric research to Yale University and has requested the Corporation of Yale University to establish the Foundations' Fund for Research in Psychiatry. The purpose of this new foundation is, in the words of the donor, "to support research into why people become mentally and emotionally ill, why they get well, how best to help them get well and how best to help them from becoming mentally and emotionally ill."

The distribution of this fund will not be confined to Yale University. Present plans contemplate that both income and principal will be expended in accordance with the stated purpose over a period of about 20 years.

The new foundation is to be administered by a scientific board of directors, not more than two of whom may be from one institution. The directors appointed by the Yale Corporation are Frederick C. Redlich, M.D., professor of psychiatry, Yale University School of Medicine,

chairman; Charles D. Aring, M.D., professor of neurology, University of Cincinnati College of Medicine; John D. Benjamin, M.D., research psychiatrist, Child Research Council, University of Colorado; Vernon W. Lippard, M.D., dean, Yale University School of Medicine; David Shakow, Ph.D., professor of psychology, University of Illinois College of Medicine; George W. Thorn, M.D., professor of medicine, Harvard Medical School, and John C. Whitehorn, M.D., professor of psychiatry, The Johns Hopkins University School of Medicine.

After the first-term appointment (two to five years), directors will be elected by the board for a term of three years but may not be reelected within less than one year.

At its initial meeting, held in New Haven on March 27 and 28, the Board of Directors discussed questions of organization and general policy. It expressed interest in the training and support of competent investigators, in the development of appropriate research methods, in encouraging the pursuit of significant problems, and in the advancement of the basic behavioral and biological sciences as related to psychiatry.

The Board invites the communication of ideas from interested sources but will not be ready to make decisions on grants for at least six months.

Dr. Sibylle Escalona, research psychologist in the Child Study Center of Yale University, was appointed executive officer of the Foundation. The temporary address of the new organization is 333 Cedar St., New Haven 11, Conn.

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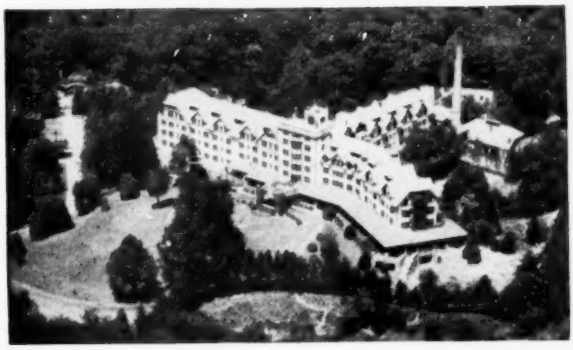

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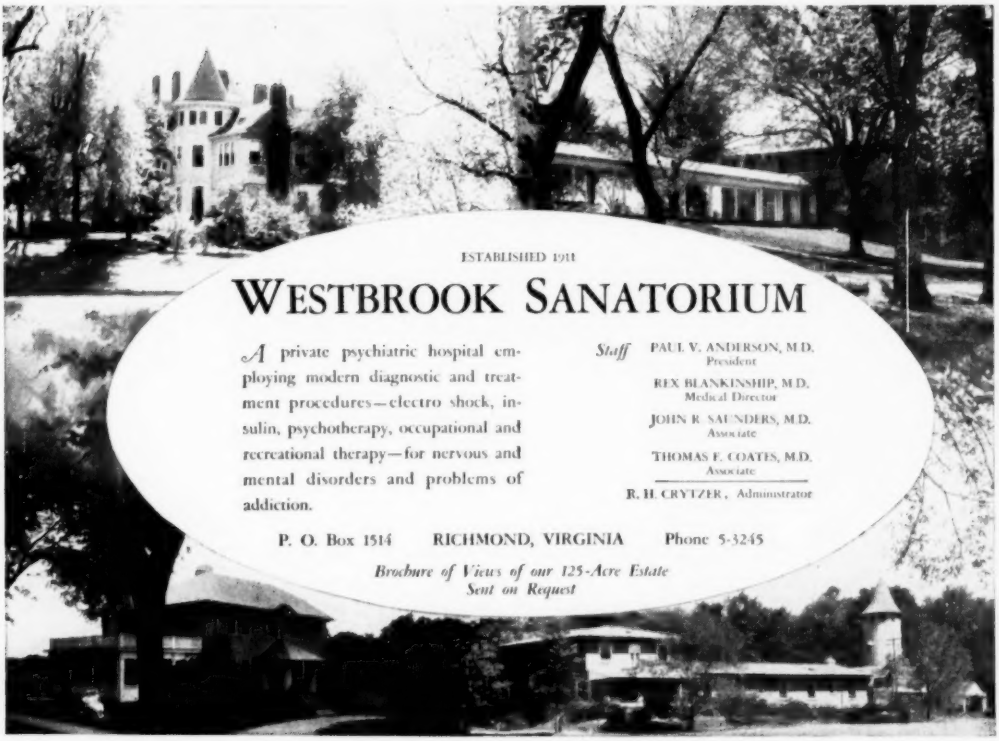
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